Hypokalaemia and xipamide

SIR,—I read the paper entitled "Ventricular fibrillation induced by xipamide" (13 February, p 494) with great interest.

We published a paper from this department in 1981,[1] in which we drew attention to the fact that xipamide, although a very effective antihypertensive agent, caused profound reductions in the serum potassium concentrations, which were potentially dangerous, and recommended that it should not be used for this purpose unless adequate potassium supplements were given at the same time.[2]

It is not clear to me, however, why the authors have included indapamide in their indictment of xipamide since their case report refers to a patient who was simply taking the latter drug and not the former. There are some chemical similarities between the two drugs, in that both are derivatives of chlorosulphonamide (xipamide is a salicylic acid derivative and indapamide an indoline derivative) but there would appear to be substantial pharmacological differences between the two.

Xipamide is undoubtedly a potent diuretic,[2] but indapamide has only minimal diuretic action when used at the recommended dosage of 2·5 mg daily.[3–5] In my own clinical experience indapamide does not produce any notable hypokalaemia, and I think it is unwise to suggest that it is as potent in this respect as xipamide without having some hard evidence to substantiate this claim. I have found indapamide to be a very useful agent in many patients who have not responded to other forms of therapy, and I think it would be a pity if it were withdrawn prematurely on the basis of a report of this kind.

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SIR,—We would like to endorse the comments made by Dr Paul Altmann and Dr J J Hamblin (13 February, p 494) on the risk of producing hypokalaemia when patients are treated with xipamide (Diurexan) and indapamide (Natrilix). Over the past six months in our hypertension clinic we have seen 20 patients who have been given indapamide, five of whom have had xipamide, though not at the same time. Hypokalaemia, defined as a serum potassium of less than 3·4 mmol(mEq)/l, was noted at least once in 10 of these. In four, despite a strong suspicion, there was insufficient evidence to incriminate directly either drug. In six cases, however, two on indapamide and four on xipamide, the temporal relationships of changing serum potassium to modifications in drug therapy strongly suggest that these drugs do cause hypokalaemia.

Indapamide. Patient 1 was referred when already taking indapamide 2·5 mg daily. The initial serum potassium was 2·9 mmol/l, and he was then put on potassium supplements (20 mmol/day). Indapamide and potassium supplements were continued for 22 months, and the mean serum potassium over this period was 3·18 (range 2·8-3·7) mmol/l. When both supplements and indapamide were stopped and chlorthalidone was substituted (without any added potassium) the serum potassium rose to 3·9 (range 3·6-4·2) mmol/l and has remained in this range since.

Patient 2 was hypokalaemic (2·9 mmol/l) on chlorthalidone. He was changed to indapamide 2·5 mg daily and was given 30 mmol/l of potassium supplements. Over the next 13 months while on this combination the mean serum potassium was 3·4 (range 2·4-4·4) mmol/l. Chlorthalidone alone was then reintroduced and given for nine months. Despite not receiving any additional potassium the mean serum concentration rose to 4·56 (range 4·1-5·2) mmol/l. At the end of this period, however, indapamide was reintroduced and the potassium fell to a mean value of 3·5 (range 3·1-4·2) mmol/l Thereafter, a change back to the conventional thiazide diuretic, bendrofluazide 5 mg daily, has been associated with a persistently normal serum potassium.

In neither patient were other changes made in therapy which might have influenced their potassium state.

Xipamide. Of the five patients treated with xipamide only one did not become hypokalaemic though the serum potassium fell from 4·7 to 3·6 mmol/l when xipamide was used to replace indapamide. This man had impaired renal function. The table shows the changes in mean serum potassium concentrations in the other four patients given xipamide 20 mg daily.

Changes in mean serum potassium concentrations in patients treated with xipamide.

Patient	Mean serum potassium before treatment (mmol/l)	Mean serum potassium during treatment with xipamide (mmol/l)	Mean serum potassium after treatment (mmol/l)
3	3·9	3·0	3·9
4	3·0	2·65	3·87
5	3·9	3·3	3·75
6	4·0	3·25	3·9

Patients 3 and 6 were on indapamide before starting xipamide, and patient 5 was given indapamide. The low initial value for patient 4 was associated with bendrofluazide therapy, and it is of interest that this presumably "susceptible" patient dropped his potassium to 2·87 mmol/l from 3·87 mmol/l when indapamide was given at a later date.

These cases were found by reviewing the notes of patients attending our outpatient clinic and do not therefore represent a controlled study. Nevertheless, we feel that our observations complement those of Dr Altmann and Dr Hamblin and suggest that indapamide and xipamide are as likely to lower the serum potassium as are other thiazide diuretics. These newer agents should therefore be prescribed for hypertension with the same degree of caution.

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SIR,—The following case of profound electrolyte disturbance with altered consciousness and multiple ventricular extrasystoles occurred after only 10 days treatment with xipamide.

A 66-year-old woman was very well on 17 February 1981 when her diuretic was changed from bumetanide 0·5 mg with potassium chloride 573 mg to 20 mg xipamide daily because her blood pressure was 220/120 mm Hg at a routine check. A week later she started to become increasingly drowsy and confused with occasional vomiting. By 26 February 1981 she was extremely drowsy and confused but with no focal neurological signs apart from an upgoing toe. Her pulse was 60 beats/min with coupled beats and her blood pressure 160/80 mm Hg. Digoxin 0·25 mg and xipamide 20 mg daily were discontinued. Her electrolyte concentrations the next morning were: sodium 104 mmol(mEq)/l; potassium 1·7 mmol (mEq)/l; bicarbonate 40 mmol(mEq)/l; chloride 44 mmol(mEq)/l; and urea 4 mmol/l (24 mg/100 ml).

She was admitted to Poole Hospital under the care of Dr D J S Sinclair and recovered with intravenous fluids and potassium. Her electrocardiogram showed digoxin toxicity with alternating bundle branch block and multiple ventricular extrasystoles. She was discharged five weeks later on frusemide 40 mg and triamterene 50 mg daily and has remained well since with normal urea and electrolyte concentrations.

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SIR,—We read with interest the case of ventricular fibrillation induced by xipamide (13 February, p 494) and entirely agree with Dr Paul Altmann and Dr J J Hamblin that both xipamide and indapamide are potent diuretics.

Indapamide (Natrilix) is included only in the antihypertensive section of the *Monthly Index of Medical Specialities* (*MIMS*), with no indication that the drug is, in fact, a diuretic and may require potassium supplementation. There have been several case reports of severe hypokalaemia in elderly patients treated with this drug.[1] We recently reported a case of ventricular tachycardia induced by hypokalaemia in a patient treated with both indapamide and xipamide.[2] Such dangerous combinations may be avoided if the diuretic properties of indapamide were clearly stated.

Although xipamide (Diurexan) has been used in many patients without the need for potassium supplementation,[3] the risks of hypokalaemia may be considerable, as demonstrated in Dr Altmann and Dr Hamblin's "Lesson of the Week." Xipamide therapy induced several attacks of hypokalaemic periodic paralysis in a patient under our care,[4] and a subsequent rechallenge with this drug confirmed its hypokalaemic properties.

Thus doctors should be aware that both these new antihypertensive agents are diuretics that may require potassium supplementation, especially in the elderly.

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How effective are our child health clinics?

SIR,—Dr W A Hendrickse (20 February, p 575) rightly points out the need for a proper evaluation of the work of child health clinics. This apart, his article does not seem to advance our state of knowledge much further, as it fails to meet the standards so comprehensively and concisely described by Fowkes and Catford.[1] Dr Hendrickse's objective was

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