Falsely High Plasma Potassium Values in Patients with Hyperaldosteronism

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Summary: The common practice of encouraging forearm exercise as an aid to venepuncture is a potent source of erroneously high plasma potassium levels. This may be sufficient to obscure a suspicion of hyperaldosteronism, with possible serious repercussions in hypertensive patients, in whom the diagnosis of hyperaldosteronism has important therapeutic implications. Plasma is preferable to serum for potassium estimations, and forearm exercise should be avoided before venepuncture for potassium measurements.

Introduction

Hypokalaemia is a common but not invariable finding in patients with adrenal-aldosterone secreting adenomas (Luetscher, 1958, 1962, 1964; Conn *et al.*, 1965, 1966; Silen *et al.*, 1966; Brown *et al.*, 1967, 1968; and see Conn, 1968). The routine estimation of plasma potassium concentration is therefore helpful in selecting those cases of hypertension in whom aldosterone estimations are desirable. If valid potassium results are to be obtained, however, it is essential to take great care both with the analytical procedures and with the techniques used for blood sampling.

A potentially major source of error arises from the common clinical practice of encouraging rhythmical fist-clenching movements in a limb to which the circulation is restricted as an aid to venepuncture. This manoeuvre has been shown to cause pronounced increases in plasma potassium concentration in normal subjects and in patients with normal potassium concentration in plasma or serum (Farber *et al.*, 1951; Skinner, 1961; Hultman and Bergström, 1962). The results reported here show that this aid to venepuncture can produce a similar increase in plasma potassium concentration in patients with hypokalaemia and thereby obscure the diagnosis of hyperaldosteronism.

Methods

Three untreated patients each with increased plasma aldosterone concentration and with either subnormal or low normal plasma potassium concentration were studied. Relevant clinical data are summarized in the Table. Large-bore needles (Gillette 19G) were placed in a central antecubital vein of each arm and 5-ml. blood samples were removed into tubes containing 150 units of lithium heparin (Teklab.) at the times indicated in Fig. I. The experimental procedure in Cases 1 and 2 was made up as follows (see Fig. 1):

Period 1: Both arms at rest; circulation unrestricted.

Period 2: Both arms at rest; sphygmomanometer cuffs around both upper arms at 100 mm.Hg.

Period 3: Right fist-clenching (about once per second for 75 seconds); left arm at rest; cuffs around both upper arms maintained at 100 mm.Hg.

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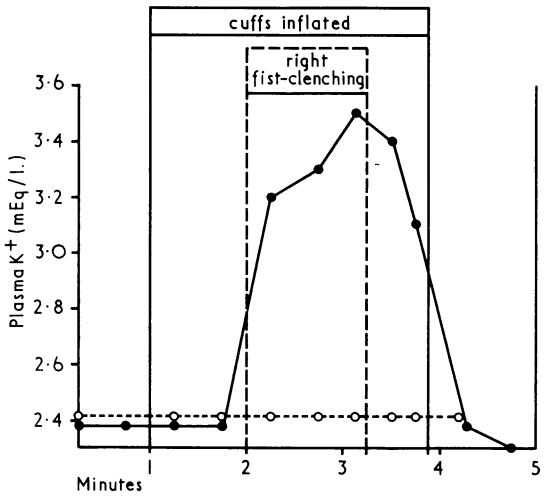

FIG. 1.—Effect of fist-clenching on plasma potassium concentration o - - - o = Plasma potassium concentration in unexercized limb. • - - - • = Plasma potassium concentration in exercized limb.

Period 4: Fist-clenching stopped—that is, both arms at rest; sphygmomanometer cuffs maintained at 100 mm.Hg.

Period 5: Both cuffs deflated; both arms at rest.

In Case 3 the same procedure was followed for the right—that is, exercised—limb, but samples were not taken from the opposite arm.

The blood samples were centrifuged within 30 minutes at 2,000 *g* for 15 minutes, the plasma was removed, spun again and the supernatant separated. Plasma potassium concentration was estimated in duplicate with the Technicon mark III Flame Photometer. The standard deviation of duplicate estimations in these experiments was 0·013 mEq/l. (n=30). Plasma aldosterone concentration was measured by a modification of the double isotope derivative technique described by Fraser and James (1968) (normal levels less than 18 ng./100 ml.) and plasma renin concentration by the method of Brown *et al.* (1964a) (normal range 4-20 units/l.).

Results

As shown in the Table a considerable rise in plasma potassium concentration occurred in blood leaving the exercising limb in each patient. In Case 1 the potassium concentration increased from distinctly subnormal levels to the lowermost part of the normal range, while in Case 2 the values increased from the lowermost to the upper part of the normal range. The increase in potassium concentration, though quite distinct, was less pronounced in Case 3. No change in potassium concentration occurred in the blood taken from the opposite

Summary of relevant clinical data

Case No.	Age	Sex	B.P. (mm. Hg)	Plasma							Diagnosis
				Aldosterone* (ng./100 ml.)	Renin* (units/l.)		Potassium (mEq/l.) Periods 1	2	3	4	5	
1	47	F.	150/90	24·6	60	Left	2·4: —	2·4:2·4	2·4:2·4:2·4	2·4:2·4	2·4: —	Secondary Hyperaldosteronism
						Right	2·4:2·4	2·4:2·4	3·2:3·3:3·5	3·4:3·1	2·4:2·3	
2	48	M.	220/120	27·0	3·6	Left	3·6:3·6	3·6:3·7	3·7:3·7:3·6	3·6:3·6	3·6:3·6	"Primary" Hyperaldosteronism
						Right	3·6:3·6	3·6:3·6	3·8:4·3:4·5	4·5:3·9	3·7:3·6	
3	18	F.	210/140	57·1	2·3	Left	— —	— —	— — —	— —	— —	"Primary" Hyperaldosteronism†
						Right	2·6:2·6	2·6:2·6	2·6:2·9:3·0	3·0:2·9	2·6:2·6	

*Blood samples taken with patients supine, after an overnight fast and during a period of constant daily intake of sodium and potassium (Na^+ fixed at a point between 139 and 144 mEq and K^+ at a point between 59 and 81 mEq/day).
†A solitary aldosteronoma was subsequently removed from the left adrenal gland with return of plasma electrolytes and blood pressure to the normal range.
—Indicates sample not taken. Blood samples for potassium determination were taken at times indicated in Fig. 1

unexercised limbs. Plasma sodium concentration did not change in these experiments.

During these experiments concurrent measurements of plasma and serum potassium concentrations in 33 normal subjects yielded the following results: serum K^+ 3·72 to 5·30 (mean 4·34, S.E. ±0·059) mEq/l.; plasma K^+ 3·60 to 5·20 (mean 4·18, S.E. ±0·061) mEq/l.; serum K^+, minus plasma K^+ = 0·10 to 0·42 (mean +0·20) mEq/l.; t=6·83, P<0·001.

Discussion

It is well established that a considerable rise in plasma potassium concentration occurs in blood removed from an antecubital vein in normal subjects and patients with normokalaemia, in response to gentle forearm exercise (Farber *et al.*, 1951; Skinner, 1961; Hultman and Bergström, 1962). This is attributed to the loss of potassium from muscle cells during exercise (see Fenn, 1936, 1940), and it is therefore not surprising that, as reported here, a similar change occurs in patients with initially low plasma potassium values. Our results indicate that the effect may be sufficient to obscure an important clue to the diagnosis of hyperaldosteronism. This is of considerable practical importance, since aldosterone measurements remain too complex for routine use, and potassium estimations are often used as part of a routine screening procedure in selecting hypertensive patients for more detailed investigation.

The frequency of this error in potassium measurements was assessed by Skinner (1961) when comparing the serum potassium values in blood taken from patients by resident hospital doctors using standard techniques, including forearm exercise, with those obtained in blood taken by himself immediately afterwards, avoiding fist-clenching. In two cases the same result was obtained, but in each of the remaining eight cases the serum potassium concentration in the blood removed by the routine clinical service exceeded that in the control samples (range +0·1 to +0·8 (mean +0·44) mEq/l.; t=3·85; P<0·01).

The effect is likely to be greater when more forceful forearm contractions are encouraged—for example, when venesection is performed by relatively inexperienced operators in patients whose veins are difficult to find. This error may have serious therapeutic implications, particularly in hypertensive patients. In such cases it is important to obtain valid measurements of potassium and to establish the diagnosis of hyperaldosteronism, since when this is due to an adrenocortical adenoma, normal blood pressure may be restored either by excising the tumour (Conn *et al.*, 1964) or by prolonged treatment with spironolactone (Brown *et al.*, 1964b, 1965, 1969a, 1969b; Spark and Melby, 1968).

Other sources of error in the estimation of circulating potassium include: leakage of potassium from red blood cells to plasma or serum and trauma of red blood cells with consequent haemolysis. Major errors due to the latter effect are probably infrequent since haemolysed samples are discarded, but mistakes due to the use of serum in preference to plasma, though well recorded, seem to be insufficiently appreciated. The potassium concentration of serum left in contact with blood cells falls slightly at first, and then increases (Kaminer and Bernstein, 1952; Hultman and Bergström, 1962). These changes were not observed with plasma containing more than 40 units of heparin per ml. for periods up to four hours (Hultman and Bergström, 1962), but a progressive rise has been observed after this time (Davies, 1968, unpublished). Pfleiderer *et al.* (1959) reported serum potassium values from 0·57 to 0·87 mEq/l. higher than concurrent plasma levels in a small group of normal subjects, and this discrepancy has been confirmed in larger series (Whitfield, 1966, and personal communication), and a highly significant difference was observed in our own laboratory (see Results).

The clinical importance of this difference was observed in a comparison of concurrently measured plasma and serum potassium concentrations in another case. In this patient, with so-called secondary hyperaldosteronism, hypertension was associated with stenosis of the right renal artery and increased plasma levels of both aldosterone (116 ng./100 ml.) and renin (110 units/l.). The concentration of potassium in serum exceeded that in plasma in 18 of the 19 concurrent measurements and on four occasions the serum levels would not have raised the possibility of hyperaldosteronism (Fig. 2). In this patient all the biochemical abnormalities and the blood pressure were restored to the normal range after removal of the right kidney.

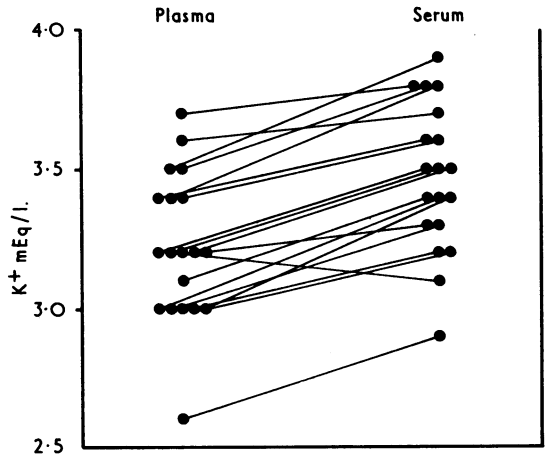

FIG. 2. Relationship between plasma and serum K+ concentration Concurrent measurements of plasma and serum potassium concentration in a patient with hypertension, unilateral renal artery stenosis, and hyperaldosteronism. Means: serum 3·47 ± 0·267; plasma 3·22 ± 0·266; t 2·87; P<0·001. Serum K minus plasma K = −0·1 to +0·4 (mean 0·25) mEq/l.

A small diurnal variation in plasma potassium concentration, with increases after meals, has been observed by some investigators (Hultman and Bergström, 1962) but not by others (Fawcett and Wynn, 1956).

With these potential sources of error in mind, the following recommendations are made concerning venepuncture for potassium estimations: (1) venous stasis is permitted but forearm exercise should be avoided immediately before and during venepuncture; (2) if forearm exercise has to be used the tourniquet should be released after venepuncture and the arm rested for two to three minutes before the blood sample is taken; and (3) plasma is preferred to serum, particularly if the blood cells cannot be separated immediately.

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REFERENCES

Brown, J. J., Davies, D. L., Lever, A. F., Robertson, J. I. S., and Tree, M. (1964a) *Biochemical Journal*, **93**, 594
Brown, J. J., Davies, D. L., Lever, A. F., Peart, W. S. and Robertson, J. I. S. (1964b) *British Medical Journal*, **2**, 1636.
Brown. J. J., Davies, D. L., Lever, A. F., Peart, W. S., and Robertson, J. I. S. (1965). *Journal of Endocrinology*, **33**, 279.
Brown, J. J., *et al.* (1967). In *Proceedings of the 3rd International Congress of Nephrology*, edited by J. S. Handler, vol. 1, p.226. Basel, Karger.
Brown, J. J., *et al.* (1968). *Lancet*, **2**, 55.
Brown, J. J., *et al.* (1969a). *Journal of Endocrinology*, **43**, IV.
Brown, J. J., *et al.* (1969b). *Proceedings of the Royal Society of Medicine*, **62**, 1258.
Conn, J., Knopf, R., and Nesbit, R. (1964). In *Aldosterone*, edited by E. E. Baulieu and P. Robel, p.327. Oxford, Blackwell.
Conn, J. W., Cohen, E. L., Rovner, D. R., and Nesbit, R. M. (1965). *Journal of the American Medical Association*, **193**, 200.
Conn, J. W., Rovner, D. R., Cohen, E. L., and Nesbit, R. M. (1966). *Journal of the American Medical Association*, **195**, 21.
Conn, J. W. (1968). *Harvey Lectures*, **62**, 257.
Farber, S. J., Pellegrino, E. D., Conan, N. J., and Earle, D. P. (1951). *American Journal of the Medical Sciences*, **221**, 678.
Fawcett, J. K., and Wynn, V. (1956). *British Medical Journal*, **2**, 582.
Fenn, W. O. (1936). *Physiological Reviews*, **16**, 450.
Fenn, W. O. (1940). *Physiological Reviews*, **20**, 377.
Fraser, R., and James, V. H. T. (1968). *Journal of Endocrinology*, **40**, 59.
Kaminer, B., and Bernstein, R. E. (1952). *South African Journal of Medical Sciences*, **17**, 35.
Hultman, E., and Bergström. J. (1962). *Scandinavian Journal of Clinical and Laboratory Investigation*, **14**, Suppl. No. 64, p. 87.
Luetscher, J. A. (1958). *Annals of Internal Medicine*, **48**, 1424.
Luetscher, J. A. (1962). In *The Human Adrenal Cortex*, edited by A. R. Currie, T. Symington, and J. K. Grant, p.479. Edinburgh, Livingstone.
Luetscher, J. A. (1964). *Medicine*, **43**, 437.
Pfleiderer, T., Otto, P., and Hardegg, W. (1959). *Klinische Wochenschrift*, **37**, 39.
Silen, W., Biglieri, E. G., Slaton, P., and Galante, M. (1966). *Annals of Surgery*, **164**, 600.
Skinner, S. L. (1961). *Lancet*, **1**, 478.
Spark, R. F., and Melby, J. C. (1968). *Annals of Internal Medicine*, **69**, 685.
Whitfield, J. B. (1966). *Journal of Clinical Pathology*, **19**, 496.

Hygiene of Infant-feeding Utensils. Practices and Standards in the Home

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Summary: Of 758 infants' feeding-bottles and teats collected aseptically by health visitors in four areas of Great Britain and examined in public health laboratories, less than two-thirds of the bottles and just over half of the teats produced results within an arbitrary "satisfactory" level. The mothers who said they used the hypochlorite method of sterilization and of storage of bottles and teats produced significantly better results. More of the mothers with satisfactory results had attended mothercraft classes. Twenty-two per cent. of babies in the sample were said to have suffered from diarrhoea, or vomiting, or both.

The standards of home sterilization of bottles and teats could be improved, and straightforward and effective health education is required, together with professional backing, so that mothers would put into practice what they had been taught.

During this century in Great Britain the infant mortality rate has steadily improved. The principal reason for this is the reduction in deaths from infectious diseases, including gastro-enteritis; one of the consequences has been the adoption by doctors, nurses, and patients of a much more complacent attitude towards preventing enteritis in infants, greater reliance being placed on efficient therapy. Much time and effort, however, is still spent, particularly by health visitors, on one aspect of prevention—namely, advising mothers of the need to sterilize baby-feeding utensils adequately. Below we consider how effectively this advice is being carried out in the home.

In an earlier study (Gatherer and Wood, 1966) it was shown that the number of mothers who knew how to sterilize bottles and teats was far in excess of the number who were actually doing it correctly. The mothers who were interviewed all lived in the same town and were a rather selected group; nevertheless, the results aroused interest and it was decided to repeat the study in a number of different areas and to use a more random sample of mothers.

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Method

Four areas in Great Britain were approached and the M.O.H.s agreed to take part: these were: Area A, a large industrial city in the north; Area B, a medium-sized town in the north; Area C, a mixed industrial and rural county in the Midlands; and Area D, a rural county in the south.

In each of the four authorities an area was selected which contained a cross-section of socio-economic groups and which was geographically convenient for the participating public health laboratory. In each area sample lists of babies aged between 2 and 4 months were drawn up.

Collection of Bottles and Teats

The health visitors undertaking the survey called without warning on the mothers at a time which they estimated would be just before the morning feed. The bottle and teat to be collected had to be, in the mother's opinion, clean and ready to be filled with the feed. The bottles and teats were placed by the mother into sterile paper bags which were previously sealed and which were opened aseptically by the health visitors. The bag and contents were delivered to the laboratory and a sterile replacement bottle and teat were given to the mother.

A short structured questionary was completed by the health visitor. Usually this was done at the time of collection of the bottles and teats. Questions were put to the mothers concerning their knowledge of and attitudes to methods of sterilization in the home.

The possibility that the results for bottles taken from hypochlorite solution could be influenced by any residual