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Five millilitres of blood were taken for drug analysis, and the plasma was separated and frozen at −21°C until analysed. Serum metformin was measured by a specific gas liquid chromatographic (GLC) method (Lennard *et al.*, 1978) in the Department of Therapeutics, Royal Hallamshire Hospital, Sheffield, U.K.

To 100 μl plasma, 20 μl buformin (10 μg/ml, as internal standard) and 5 ml acetonitrile were added. After mixing on a vortex for 1 min, the mixture was centrifuged for 2–5 min at 3000 rev/min. The supernatant was decanted into a conical tube and evaporated to dryness on a vortex evaporator at 50°C.

One hundred microlitres of amylacetate and 10 μl chlorodifluoroacetic anhydride were then added and the solution vortexed for 1 min. Nine and a half millilitres of 4 M NaOH were then added, the mixture vortexed, and then centrifuged for 1 min at 3000 rev/min.

Of the top layer, i.e. the amylacetate layer, 0.2 μl was then injected into the GLC. For calibration, metformin solutions of 1 μg/ml and 10 μg/ml, and buformin solution of 10 μg/ml were used.

The GLC conditions used were:
Detector temperature 325°C
Injector temperature 225°C
Column temperature 190°C
Range X 512
N_2 1.35 kg/C_m3
Flow rate 50 ml/min
Detector current 10 (half runaway current)

The assay was done in duplicates because of variable peaks. The peak height ratios of metformin to buformin were calculated and metformin concentrations read off the calibration curve.

Results

The age and sex distribution of the sixteen patients is shown in Table 1. There were eleven males and five females giving a M:F ratio of 2:1. The detailed clinical and serum level data on all patients are shown in Table 2. The mean age for all patients was 50.69 ± 7.3 (50.9 ± 8.69 in males and 50.2 ± 3.27 in females). The mean weight was 61.29 ± 12.66 (60.12 ± 19.09 in males, 63.82 ± 9.65 in females). The mean serum level of metformin was 512 ± 485.2 ng/ml. The mean corrected dose was 25.42 ± 5.02 mg/kg. There was a two-fold variation in the corrected daily dose and a thirty-eight-fold variation in the serum level (50–1886 ng/ml). All patients had taken metformin for longer than 6 months and all had normal serum creatinine.

TABLE 1. Serum metformin levels in Nigerian diabetics: age and sex Distribution

Age (years)	Sex		Total
	M	F	
31–40	1	–	1
41–50	7	3	10
51–60	2	2	4
61–70	1	–	1
Total	11	5	16

There was no correlation between the serum metformin concentration and the age, weight, corrected daily dose and blood sugar levels.

Discussion

The range of serum metformin levels obtained in this study (50–1886 ng/ml) is similar to that obtained by Sirtori *et al.* (1978) in a study in Italians. The range in their study was between 60–2240 ng/ml and the mean level in patients on three tablets a day was 382.3 ± 76.9 compared to a mean of 512 ± 485.2 ng/ml in this study. The mean level obtained in their patients on two tablets a day was 384 ± 62.4 ng/ml which was practically the same as in those on three tablets a day, although the number studied was small. Unlike in their study, we did not observe any correlation between dose of metformin administered (calculated as mg/kg body weight) and the steady state plasma levels.

However, Tucker *et al.* (1981) in studies carried out on British subjects, have shown that a steady state plasma metformin level of 2–3 μg/ml (2000–3000 ng/ml) should be expected when doses of 1–5 g/day are administered. If this is indeed universally applicable, the levels obtained in our patients on 1.5 g/daily were very low. The highest level obtained was 1886 ng/ml and seven of our patients (43.7%) had levels less than 200 ng/ml and only two (12.5%) had values higher

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SERUM METFORMIN LEVELS IN NIGERIANS WITH NON-INSULIN-DEPENDENT DIABETES MELLITUS

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Summary

'Steady state' serum concentrations of metformin have been measured in sixteen Nigerians with non-insulin-dependent diabetes mellitus. There was a thirty-eight-fold variation in the serum levels (50–1886 ng/ml). The mean serum level of metformin was 512 ± 485.2 ng/ml. This compared favourably with the mean levels (382.3 ± 76.9 ng/ml) obtained in a similar study in Italians.

The observed levels however fell far short of those expected in patients on 1–5 g metformin daily. The role of poor bioavailability *vis-à-vis* poor patient compliance deserves further detailed pharmacokinetic study.

Résumé

Des concentrations du sérum de metformin en état stable ont été mesurées en appliquant une méthode chromatographique à liquide de gaz sur seize Nigériens affligés de non-insuline dépendant diabète sucré. Il y avait trente-huit variations dans les niveaux de sérum (50–1886 ng/ml). Le niveau moyen du sérum de metformin était 512 ± 485.2 ng/ml. Ceci ne le cède en rien au niveau moyen (382.3 ± 76.9 ng/ml) obtenu au cour d'une étude du même ordre sur les italiens.

Les niveaux observés étaient bien au-dessous de ceux prévus chez les patients avec 1–5 g de metformin par jour. Le rôle de la pauvre disponibilité vis-à-vis la pauvre complaisance des malades mérite une nouvelle étude pharmacokinétique détaillée.

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Introduction

Metformin, a biguanide, is used, most often, in the Diabetic Clinic of the University College Hospital, Ibadan, as a second oral hypoglycaemic drug in patients not responding to 500 mg daily dose of chlorpropamide. It is usually given in a daily dose of 1.5 g, i.e. as 500 mg thrice a day. Many of our patients on full doses of chlorpropamide and metformin are often in poor control of their diabetic state. Very many factors may be responsible for this and these include poor bioavailability, poor patient compliance and inter-individual differences in the handling of these drugs. We have measured serum metformin levels in some of our patients to find out their steady state serum concentrations and to compare these with those published in the limited literature on metformin pharmacokinetics.

Materials and methods

The study was carried out in a total of sixteen Nigerian diabetic patients, fifteen of whom were also taking chlorpropamide 500 mg daily. The name, age, sex, height, weight, date of diagnosis, other medical problems, drugs being taken, dosages, duration of therapy and time last dose and last meal were taken were all recorded for each patient. Blood was then taken for blood sugar, electrolytes and urea, serum creatinine, and liver function tests.

than 1000 ng/ml. This observation would be due to a number of factors which may include poor patient compliance with drug regimen or poor bioavailability of the brand of metformin commonly available here – 'glucophage'. It should be pointed out, however, that chemist retailers in this country have been known to sell out-dated drugs to patients (most of whom are illiterates), and little is yet known about the effects of the hot, humid environment of the tropics on the shelf life of most drugs exported to developing countries. It would be observed that eight of the patients (50%) were classified as poorly controlled and the blood sugar values in many of these patients were strikingly and unacceptably high. Because of the peculiarities of this environment, as in most other developing countries, i.e. high illiteracy rate, poverty, poor social amenities, non-availability or difficulty in procuring insulin, we always feel obliged to establish failure of oral hypoglycaemic agents in most of our diabetics, especially the non-insulin-dependent ones, before we embark on insulin therapy. We cannot afford the luxury of a liberal insulin treatment policy, and any patient on insulin truly requires it. This means that oral hypoglycaemic agents, both sulphonylureas and biguanides will for a long time continue to be a mainstay in the management of our diabetics. It is therefore, imperative that we continue to look closely into those factors or variables which may be limiting their usefulness or efficacy.

Although these findings relating to plasma levels of metformin are preliminary, they do suggest the need to study more closely the pharmacokinetics of metformin not only in Nigerian diabetics but probably also in healthy subjects as well so that the question of relative contribution of probable poor bioavailability or poor patient compliance to the observed low levels can be resolved.

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TABLE 2. Serum metformin levels in Nigerian diabetics: individual parameters

No.	Name	Age (years)	Sex	Weight (kg)	Daily dose (mg tds)	Corrected dose (mg/kg)	Last dose taken	Blood sugar (mg/ 100 ml)	Serum level of metformin	Control of diabetes mellitus	Other drugs
1	J.O.	40	M	54	500	27.78	Same day	338	1886	Poor	Chlorpropamide
2	S.O.	69	M	58	500	25.86	Same day	118	640	Fairly good	Chlorpropamide
3	J.T.	51	F	79	500	18.99	2 days prior	148	50	Poor	Chlorpropamide
4	A.A.	60	M	47	500	31.91	Same day	382	940	Poor	Chlorpropamide
5	S.K.	50	M	51.5	500	29.13	Same day	230	115	Poor	Chlorpropamide
6	A.R.	55	F	58.8	500	25.51	Same day	121	815	Fairly good	Chlorpropamide
7	K.S.	50	M	65.4	500	22.94	Same day	84	140	Good	Chlorpropamide
8	O.S.	46	F	67.5	500	22.22	Same day	102	440	Good	Chlorpropamide
9	O.D.	45	M	90	500	16.67	Same day	109	525	Good	–
10	K.S.	50	F	58.8	500	25.51	Day before	298	130	Poor	Chlorpropamide
11	O.L.	41	M	56.2	500	26.69	5 days prior	395	112	Poor	Chlorpropamide
12	B.O.	59	M	66.2	500	22.66	Same day	682	590	Poor	Chlorpropamide
13	O.A.	49	F	55	500	27.27	Same day	204	480	Poor	Chlorpropamide
14	E.M.	50	M	78	500	19.23	Same day	112	195	Fairly good	Chlorpropamide
15	A.Y.	46	M	41	500	36.59	Same day	104	1024	Good	Chlorpropamide
16	F.R.	50	M	54	500	27.78	Same day	98	110	Good	Chlorpropamide