of addicts in which a drug was implicated were due to medically prescribed drugs: barbiturates in the earlier years of the study and more recently "other opiates," mostly dipipanone hydrochloride and dextromoramide. This in no way minimises the problem presented by illicitly imported drugs. Their easy availability may provide the stepping stone into drug abuse and addiction for a large number of young people, and it is essential that as far as possible these drugs should be kept out of the country.

These findings are not confined to the deaths of notified addicts as they are similar to the results of studies carried out in coroners' courts into deaths due to addiction. In one such study 41% of the deaths were of addicts not known to the Home Office.[1]

By definition, mortality studies deal with the most serious forms of addiction, from which the patient dies. What is apparent from our findings is that prescribed drugs rather than illicitly imported drugs are at the core of this aspect of the problem. Far from being a new phenomenon, prescribed drugs have always played a large part in addiction in Britain, and this may be the inevitable consequence of a medical, rather than a criminalising, response to addiction. Whatever the underlying reasons, the fact that prescribed drugs are causing so many deaths of addicts demands a response from the medical profession from whom these drugs originate. An active system of monitoring is the first requirement to identify new drugs of abuse before they have become entrenched in the black market.

This study has shown the value of one particular source of information, the Home Office index, in investigating and identifying serious problems of addiction.

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Epidemiological characteristics of platelet aggregability

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Abstract

The epidemiological characteristics of platelet aggregability were established in 958 participants in the Northwick Park Heart Study. The main analyses were based on the dose of adenosine diphosphate at which primary aggregation occurred at half its maximum velocity. Aggregability increased with age in both sexes, was greater in whites than blacks (particularly among men), and tended to decrease with the level of habitual alcohol consumption. Aggregability was, however, greater in women than men and in non-smokers than smokers. There was no relation between aggregability on the one hand and obesity, current or past oral contraceptive use, menopausal state, or blood cholesterol and triglyceride concentrations on the other. Aggregability was somewhat, though not significantly, higher in men with a history of ischaemic heart disease and in those with electrocardiographic evidence of ischaemia than in those without. There was a strong association between the plasma fibrinogen concentration and aggregability.

The widely held concept of platelet aggregability and its implications is probably an oversimplification. In the prevention of thrombosis it may be as useful to consider modifying external influences on platelet behaviour, such as plasma fibrinogen concentration or thrombin production, as it is to rely solely on platelet active agents.

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Introduction

The role of platelets in thrombosis has been the subject of numerous studies for many years, especially over the past two decades. There is, however, no established measure of in vivo platelet function by which those at high risk of thrombosis can be characterised. In 1962 Born described a method for studying platelet aggregation that was based on changes in the optical density of a suspension of platelets.[1 2] This method, or modifications of it, has since been widely used in laboratory and clinical studies on the assumption that ready aggregability is an index of susceptibility to thrombosis. Here we describe the epidemiological characteristics of platelet aggregability seen in the Northwick Park Heart Study, a prospective study of the role of the haemostatic system in the pathogenesis of arterial disease.

Subjects and methods

SUBJECTS

Fuller details of the Northwick Park Heart Study have been published elsewhere.[3-7] In summary, 3500 participants were recruited

between 1972 and 1978 from various occupational groups in north west London. In 1978 follow up began, and dose response aggregometry[1,2] was introduced using adenosine diphosphate and adrenaline as aggregating agents. The present report is based on results from 958 participants whose blood samples were the first to undergo aggregometry. This group comprised 685 men (635 white, 50 black) and 273 women (246 white, 27 black). Of the white men, 24 had previously had episodes of ischaemic heart disease manifesting as myocardial infarction or angina. There was electrocardiographic evidence of possible ischaemia (Minnesota codes 1.1-1.3, 4.1-4.4, 5.1-5.3, or 7.1) in 54.

Nearly all participants were seen between 0700 and 1100. Each was given a list of fatty foods to avoid at breakfast on the day of examination together with a suggested low fat menu. Compliance with these instructions was generally good. Blood was taken without venecompression unless otherwise unobtainable. Nine volumes of blood were added to one volume of 3·13% trisodium citrate.

Of the 958 participants, 542 were seen at this hospital and the remaining 416 at their place of work, about seven miles away. The results from the two groups were combined as the adenosine diphosphate ED50 (see below) does not differ according to the interval between blood sampling and testing within the periods used in this study.[8]

LABORATORY METHODS

The platelet count of the platelet rich plasma was adjusted to 250 000/μl with autologous platelet poor plasma. The 10 doses of adenosine diphosphate used ranged in final concentration from 5×10^{-5}M to 1×10^{-7}M and the eight doses of adrenaline from 5×10^{-5}M to 5×10^{-8}M. Rates of primary aggregation were expressed as change in light transmittance in units per minute and were measured at the steepest initial part of the curve.[8]

The sigmoid relation between log dose of aggregating agent and primary aggregation rate was fitted using a computer program.[8] Two parameters were measured and are illustrated in the stylised sigmoid (fig 1). The estimated maximum response is the maximum

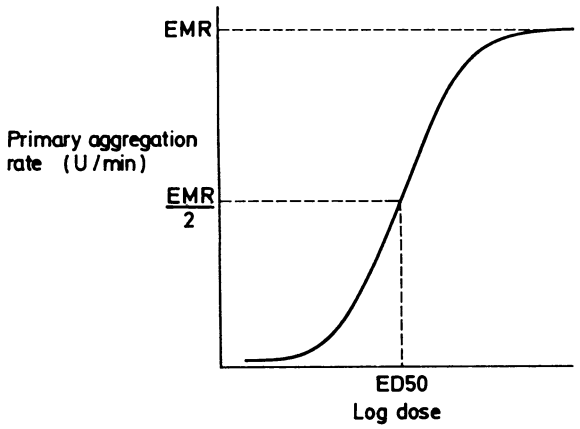

FIG 1—Stylised dose response curve, with EMR indicating estimated maximum response and ED50 dose of reagent giving half estimated maximum response (EMR/2).

response that could be expected—that is, the asymptotic value. It is a measure of velocity; the higher it is the more aggregable the platelets. The ED50 is the estimated dose of an aggregating agent that gives a response of half the estimated maximum response; the lower the ED50 the more aggregable the platlets. The main emphasis in this paper is on results using the ED50 for adenosine diphosphate, which is subject to considerably less laboratory error[8] than the other parameters. The geometric mean adenosine diphosphate ED50 for the 958 subjects was $9\cdot0\times10^{-7}$M (95% range, 3·6 to $22\cdot5\times10^{-7}$M).

STATISTICAL ANALYSIS

In multiple linear regression analyses of the estimated maximum response and log ED50 we used forward stepwise selection of variables with a critical p value of 0·05, and checking in cases of difficulty was by backwards stepwise and "best subsets" methods.[9,9a] To allow for possible time trends in the measurement of the parameters of platelet aggregation, change points were included as extra variables in the regressions, as described elsewhere.[10] The results shown in the figures represent unadjusted data, except in figure 8, but the p values given (which are exact down to 10^{-4}, below which $p<10^{-4}$ is quoted) are derived from the multiple regression analyses. Possible sex differences in the relation between a variable and aggregability were assessed by establishing the relevant interaction between sex and that variable.

Results

Figure 2 shows the correlations between the four parameters. All the correlations were significant at p = 0·01 at least.

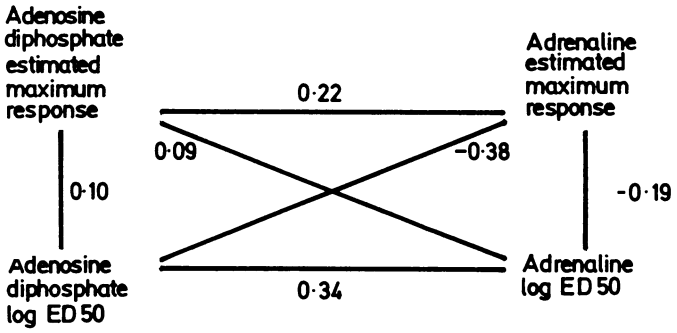

FIG 2—Correlations (r) between four measures of platelet aggregability.

Figure 3 shows the relation between aggregability and age. Aggregability increased—that is, ED50 decreased—with advancing age, and the increase, of about 8% per decade, was highly significant ($p<10^{-4}$). The increase with age may have been greater in men than women, though the difference in rate of increase between the sexes was not significant (p = 0·12). At all ages aggregability was substantially less in men than in women, by about 24% overall ($p<10^{-4}$). Haemoglobin and packed cell volume were strongly and positively associated with adenosine diphosphate ED50 and both were, of course, higher in men than women. To allow for haematological differences between the sexes that affect the measurement of aggregability haemoglobin concentrations and packed cell volumes were included in a multiple regression analysis. The result was to reduce the difference in adenosine diphosphate ED50 between the sexes by about half, but the difference remained highly significant ($p<10^{-4}$).

Figure 4 shows the differences between whites and blacks. In both sexes, but particularly in men, aggregability was less in blacks than in whites ($p<10^{-4}$ overall, p = 0·02 for interaction of sex with ethnic group).

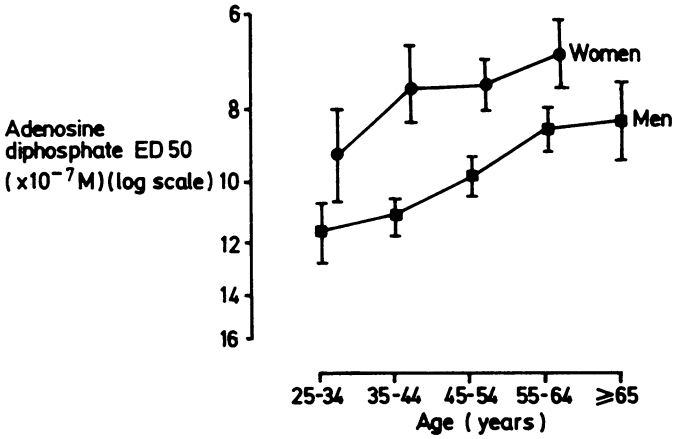

FIG 3—Adenosine diphosphate ED50 by age and sex, showing means with 95% confidence intervals.

Figure 5 shows the differences between cigarette smokers and non-smoknon-smokers. Particularly in men, aggregability was less in smokers than non-smokers ($p=0.005$ overall, $p=0.66$ for interaction of sex with smoking). There was little evidence of a dose response effect among the smokers according to the stated number of cigarettes smoked.

Figure 6 shows the relation between adenosine diphosphate ED50 and average stated daily alcohol consumption. Aggregability tended to be less the heavier the consumption ($p=0.06$ overall).

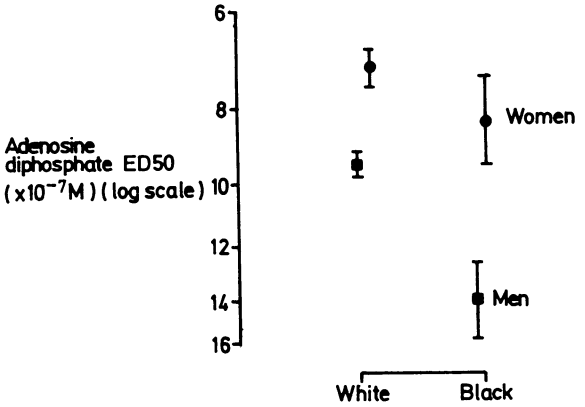

FIG 4—Adenosine diphosphate ED50 by ethnic group and sex, showing means with 95% confidence intervals.

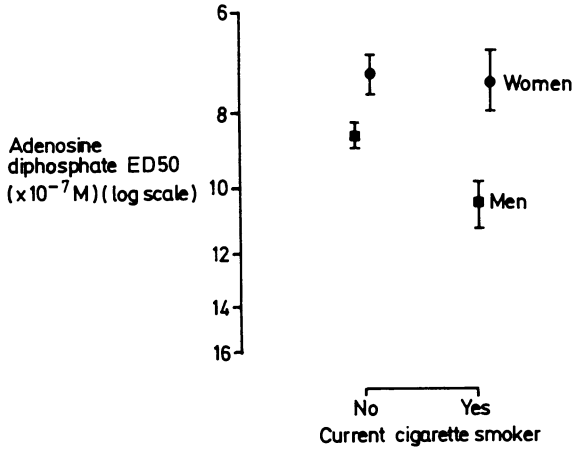

FIG 5—Adenosine diphosphate ED50 by smoking habit and sex, showing means with 95% confidence intervals.

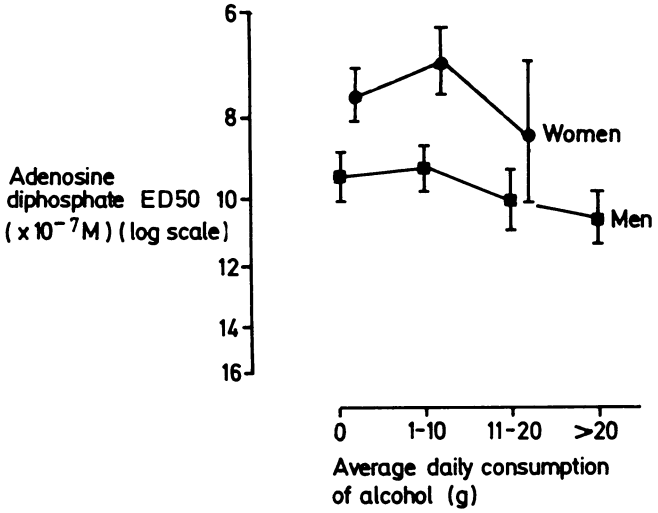

FIG 6—Adenosine diphosphate ED50 by alcohol consumption and sex, showing means with 95% confidence intervals.

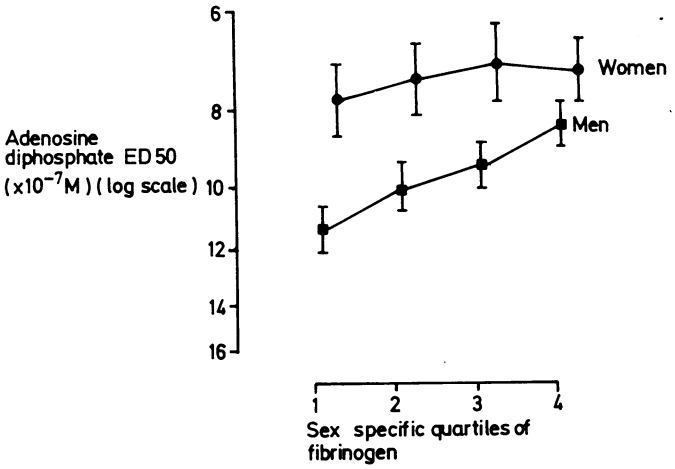

FIG 7—Adenosine diphosphate ED50 by sex specific quartile (1=low) of fibrinogen concentration, showing means with 95% confidence intervals.

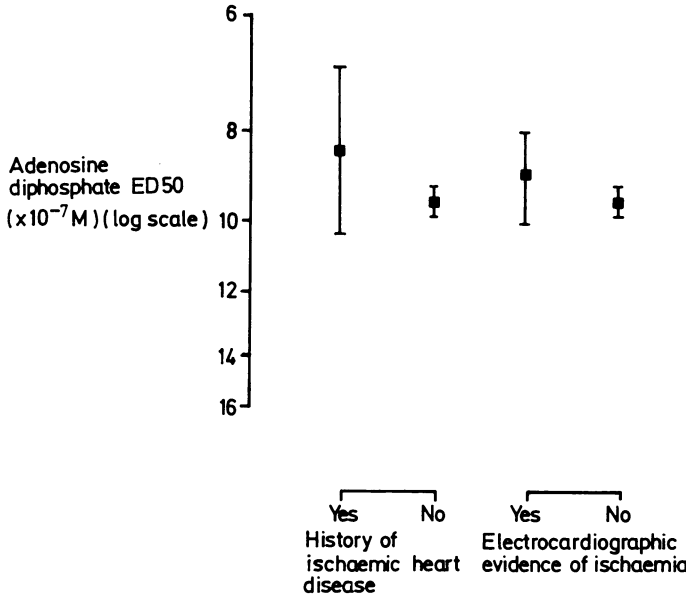

FIG 8—Age adjusted adenosine diphosphate ED50 in white men (n=635) by presence or absence of electrocardiographic abnormalities and history of ischaemic heart disease, showing means with 95% confidence intervals.

Figure 7 shows increasing aggregability with rising plasma fibrinogen concentrations ($p<10^{-4}$). The relation appeared to be stronger in men than women, though the interaction of sex with fibrinogen concentration was not significant ($p=0.11$).

In terms of adenosine diphosphate ED50, aggregability was not significantly related to: recent consumption of aspirin; obesity; current or past use of oral contraceptives or menopausal state; or blood concentrations of cholesterol or triglycerides. (It is secondary aggregation that is inhibited by aspirin.)

Figure 8 summarises the findings, adjusted to age 50, by history of ischaemic heart disease or electrocardiographic abnormality in the white men. Adenosine diphosphate ED50 was somewhat, but not significantly, lower—that is, platelets were more aggregable—in those with ischaemic heart disease ($p=0.15$) and those with electrocardiographic abnormalities ($p=0.19$) than those without.

The table summarises the epidemiology of adenosine diphosphate ED50 and the other three parameters. With two exceptions, the associations established by the other parameters were consistent with the findings based on adenosine diphosphate ED50. The exceptions were the falls in adenosine diphosphate estimated maximum response—that is, less aggregable platelets—with increasing age and with increasing fibrinogen concentrations. The effect of alcohol was more convincingly shown with the adrenaline parameters than with adenosine diphosphate ED50.

Epidemiological characteristics of four measures of platelet aggregability

	Adenosine diphosphate		Adrenaline	
	Estimated maximum response	ED50	Estimated maximum response	ED50
Age: Young→old	− −	− − −	+ + +	−
Sex: Men→women	+	− − −	+ + +	−
Race: white→black		+ + +	− − −	
Smoking: Non-smokers→smokers	−	+ +	− −	
Alcohol consumption: none→heavy		+	−	+ +
Fibrinogen: Low→high	− − −	− − −		

Signs give direction of change, according to progression indicated by arrow. For example, adenosine diphosphate ED50 decreases with advancing age but is higher in blacks than whites. Three signs indicate strong effects (typically $p < 0.005$); two signs indicate convincing but weaker effects (typically $0.01 > p > 0.005$); one sign indicates marginal effects (typically $0.1 > p > 0.01$); blanks indicate no apparent effect. (NB For estimated maximum response + indicates increased aggregability (and vice versa); for ED50—indicates increased aggregability (and vice versa).)

Discussion

The results and interpretation of aggregation studies will depend to an extent on the aggregating agent and parameter used. Different parameters may indicate different aspects of platelet behaviour. Two of the correlations, each with adenosine diphosphate estimated maximum response (with adenosine diphosphate ED50 and with adrenaline ED50), seemed anomalous, the suggestion of increased aggregability using one being associated with the suggestion of decreased aggregability using the other.

Theoretical arguments can be advanced for preferring other measures of platelet activity, such as whole blood aggregation or platelet specific proteins, over the method used here. Until, however, there are adequate prospective data on different indices of platelet behaviour and their relation with the incidence of ischaemic heart disease, such arguments must indeed be regarded as theoretical. One reason for establishing the epidemiological characteristics of aggregability by the Born technique is the great extent to which it and its modifications have been used coupled with the underlying assumption that ready aggregability implies increased thrombotic risk. Another is that the method to some extent mimics the early stages of platelet activity in haemostasis and thrombosis. Adenosine diphosphate almost certainly has a role in primary haemostasis in animals[11] and man.[12]

Aggregability measured by adenosine diphosphate ED50 increased with advancing age, and this was consistent with the increase in the incidence of ischaemic heart disease with age.

All four parameters were consistent in indicating that aggregability is greater in women than men. This finding, which was lessened but not eliminated by taking sex differences in haemoglobin concentration and packed cell volume into account, was in line with the suggestions of other smaller studies.[13–15] Antiaggregating agents appear to be more effective in men than women,[16 17] and most of the associations indicated by our data are, or appear to be, more considerable in men.

The much greater aggregability in white than black men, with a similar though less striking difference among women, was consistent with the higher incidence of ischaemic heart disease in whites.

Our results on habitual cigarette smoking were unexpected, showing that in terms of adenosine diphosphate ED50 cigarette smokers, particularly men, have less aggregable platelets than non-smokers. This finding was contrary to the results of smaller studies of the immediate effects.[18–20] The other results by smoking habit (table) were generally consistent with the adenosine diphosphate ED50 finding. The relation between alcohol consumption and adenosine diphosphate ED50, supported by the results using the adrenaline parameters (table), was consistent with the results of other studies[21 22] and with the possibility that moderate alcohol consumption confers some protection against ischaemic heart disease.[23]

It has been suggested that sensitive platelets may form aggregates in vivo or during the preparation of platelet rich plasma.[24] They might therefore not be as available in men as they are in women at the stage of aggregometry. This could explain the apparently anomalous difference in aggregability between men and women. A similar explanation could be suggested for the results of cigarette smoking. If this proposition were correct, however, aggregability would presumably fall with advancing age and would probably also be greater in blacks than whites.

Aggregability measured by adenosine diphosphate ED50 increased with increasing plasma fibrinogen concentrations (fig 7). It is well known that there is a minimum requirement for fibrinogen in aggregation.[25–27] Our data suggest a steady increase in aggregability across the full physiological range of fibrinogen concentrations. High fibrinogen concentrations have been associated with an increased risk of death from cardiovascular disease.[4] This association, now reported in two other studies,[28 29] could be partly explained by the effect of fibrinogen on platelet aggregability. Some support for this hypothesis is provided by the observation that defibrination reduces the numbers of circulating platelet aggregates.[30] These indications raise the question of the extent to which differences in alleged aggregability in many clinical and laboratory studies may in fact have been due to differences in fibrinogen.

Others have reported increased aggregability in patients with hyperlipidaemia.[31 32] Our data, however, suggest no association between cholesterol or triglyceride concentrations and aggregability. It is often assumed that those with ischaemic heart disease or other manifestations of arterial disease have more aggregable platlets than those without. Our data provide only qualified support for this conclusion. Furthermore, the relation between aggregability and arterial disease[33] is by no means consistent.

The widely held concept of aggregability as an intrinsic characteristic of the platelets themselves may be a considerable oversimplification. Fibrinogen concentrations are high in those with, or at increased risk of, arterial disease in the coronary, cerebral, or peripheral circulation.[4 29 34] If platelet function is determined to any appreciable extent by external influences such as plasma fibrinogen concentration[35] and thrombin production it may be as useful to consider modifying these influences as it is to rely solely on platelet active agents.

We thank Professor G V R Born for his advice and help. This work was supported in part by the Overweight and Heart Disease Research Trust.

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SHORT REPORTS

Falsely raised plasma digoxin concentrations in liver disease

Digoxin, a cardiac glycoside, is an important drug in the management of heart failure and arrhythmias. Because of its high toxicity and narrow therapeutic range of values, monitoring digoxin concentrations in serum is important.[1] Recently, an endogenous substance causing false positive digoxin immunoassay measurements has been detected in adults with renal impairment[2] and in premature infants.[3] The magnitude of the increase in this digoxin like immunoreactive substance in some of the these patients is enough to compromise the usefulness of a measured value for digoxin. We and others have shown that large amounts of digoxin like immunoreactive substance are present in bile (unpublished observations; M R Pudek, S Vasdev, personal communication). This observation prompted us to measure the apparent concentration of digoxin in the plasma of patients with liver disease.

Patients, methods, and results

Plasma was obtained from seven patients at the Ottawa General Hospital who had clinical and biochemical evidence of liver disease. None of the patients had impaired renal function or were receiving digoxin. The table summarises the clinical diagnosis, medications, and relevant laboratory values in these patients. Digoxin was measured in plasma by both radioimmunoassay (two different manufacturers: NML Laboratories Inc, Dallas, and Abbott Laboratories, Chicago) and fluorescence polarisation immunoassay (TDX, Abbott Laboratories). The lower limit of detection by radioimmunoassay is 0·3 nmol/l (0·23 ng/ml) and by fluorescence polarisation 0·3 nmol/l. Bilirubin does not interfere with either method. The normal (therapeutic) range for digoxin in our laboratory is 1·0-2·6 nmol/l (0·8-2·0 ng/ml).

The table shows the values for plasma digoxin by both methods. The presence of digoxin like immunoreactive substance (measured by radioimmunoassay) occurred in all the patients. There was no apparent correlation between the degree of hyperbilirubinaemia and the concentration of digoxin like immunoreactive substance measured by radioimmunoassay.

Comment

The presence of an endogenous substance causing falsely raised plasma digoxin concentrations has been reported in premature infants and patients with renal failure.[2 3] Our study shows that this digoxin like immunoreactive substance is present in the plasma of patients with liver disease. The magnitude of the increase in digoxin like immunoreactive substance is enough to compromise the usefulness of a measured value of digoxin in the clinical management of a patient with liver disease who requires digoxin.

Clinical and laboratory details of patients with liver disease, together with digoxin concentrations

Case No	Age and sex	Clinical diagnosis and medications	Relevant laboratory values*	Digoxin (nmol/l)		
				Radioimmunoassay		Fluorescence polarisation immunoassay (Abbott Laboratories)
				NML Laboratories Kit	Abbott Laboratories Kit	
1	46 M	Parenteral nutrition associated cholestasis	Total bilirubin 100 μmol/l (5·8 mg/100 ml), ALP 788 U/l, AST 50 U/l, ALT 50 U/l, creatinine 67 μmol/l (0·8 mg/100 ml)	0·3	<0·3	<0·3
2	44 F	Hepatic metastases, tobramycin	Total bilirubin 196 μmol/l (11·5 mg/100 ml), AST 118 U/l, ALT 77 U/l, ALP 184 U/l, creatinine 143 μmol/l (1·6 mg/100 ml)	0·4	<0·3	<0·3
3	60 M	Alcoholic cirrhosis	Total bilirubin 147 μmol/l (8·6 mg/100 ml), ALP 247 U/l, AST 80 U/l, ALT 53 U/l, creatinine 92 μmol/l (1·0 mg/100 ml)	1·4	0·7	<0·3
4	70 F	Carcinoma pancreas, tobramycin	Total bilirubin 840 μmol/l (49·1 mg/100 ml), ALP 1500 U/l, AST 35 U/l, ALT 57 U/l, creatinine 182 μmol/l (2·1 mg/100 ml)	0·6	<0·3	0·3
5	43 M	Morbid obesity, fatty liver	Total bilirubin 113 μmol/l (6·6 mg/100 ml), ALP 158 U/l, AST 220 U/l, ALT 314 U/l, creatinine 112 μmol/l (1·3 mg/100 ml)	0·4	<0·3	<0·3
6	62 F	Brain tumour, parenchymal liver disease (cause unknown), carbamazepine	Total bilirubin 96 μmol/l (5·6 mg/100 ml), ALP 670 U/l, AST 248 U/l, ALT 570 U/l, creatinine 28 μmol/l (0·3 mg/100 ml)	0·4	<0·3	<0·3
7	59 F	Metastatic liver disease	Total bilirubin 125 μmol/l (7·3 mg/100 ml), ALP 196 U/l, AST 185 U/l, ALT 59 U/l, creatinine 111 μmol/l (1·3 mg/100 ml)	0·9	0·6	<0·3

*Normal ranges: total bilirubin 2-26 μmol/l (0·1-1·5 mg/100 ml), alkaline phosphatase (ALP) 45-125 U/l, aspartate aminotransferase (AST) 7-40 U/l, alanine aminotransferase (ALT) 7-40 U/l, creatinine 70-130 μmol/l (0·8-1·5 mg/100 ml).
Conversion: SI to traditional units—Digoxin: 1 nmol/l ≈ 0·8 ng/ml.