Computers in Medicine

Use of Computer-assisted Model in Diagnosis of Drug Hypersensitivity Jaundice

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Summary

Of 374 patients with jaundice seen in the liver unit over a four-year period 21 were finally thought to be hypersensitive to one of seven different drugs. The clinical, laboratory, and histological features were often difficult to distinguish from those of viral hepatitis, tumour of the extrahepatic biliary tree, or primary biliary cirrhosis. A computer-assisted diagnostic model made use of minor differences, and made a correct diagnosis in all patients. Even when information about drug ingestion was left out it was still correct in 81% of patients. Sixty-four other patients gave a history of ingestion of potentially hepatotoxic drugs of whom 62 were correctly diagnosed by the computer. In the complete series of 374 patients only two were incorrectly computed to have drug jaundice when there was no history of drug ingestion.

Two additional patients became jaundiced after exposure to drugs, but were found to have primary biliary cirrhosis.

Introduction

Of the drug reactions reported to the Committee on Safety of Medicines since 1968, 8% have been on account of presumed drug jaundice, while two of the four preparations withdrawn from use on the advice of the Committee were because of jaundice.¹ Because of the similarity of the clinical picture of jaundice due to drug hypersensitivity to jaundice due to other causes, diagnosis is difficult and depends largely on eliciting a drug history and exclusion of other causes.²⁻⁴ Since 1968 we have been investigating the use of a computer-assisted model in the diagnosis of jaundice.⁴ In this paper we consider the value of this approach in patients with jaundice attributed to drug hypersensitivity and compare patients in whom this was the final diagnosis with other jaundiced patients having viral hepatitis, carcinoma of the extrahepatic biliary tree, and primary biliary cirrhosis, with which they are often confused.

Patients and Methods

For the computer-assisted model, only data available within 48 hours of admission are used. These consist of 45 items of information from the history, 12 relating to physical signs, and a maximum of 34 laboratory results. In some patients 11 items from the ^{99m}Tc hepatic scintiscan were available. Histological appearances of liver biopsy specimens are not used by the model at present. The diagnosis is made in the form of a probability diagram, in which the prior probability of each of the 11 diseases—that is, the prevalence in the patients already seen—is first plotted, and the computer program selects from the information which may be obtained on a new patient those items which should progressively increase the probability of the correct disease. After the selection of each item, the next is selected on the basis of the result just obtained. The process continues until either all the information has been entered or until a final probability of > 96% certainty for any one disease is reached.

In the patients reported here the final diagnosis was presumed to be drug hypersensitivity jaundice only when there was a history of recent ingestion of a drug reported to cause this, and when other causes of jaundice had been excluded. Patients with drug jaundice from predictable hepatotoxins, such as paracetamol⁵ or norethandrolone,⁶ were excluded from this study. All patients with fulminant hepatic failure, whether of presumed toxic or viral aetiology, were also excluded. The data were looked at in two ways. Firstly, the information on each patient that had been available within 48 hours of admission was entered in the computer and used to make a diagnosis by simple reclassification.⁷ Secondly, the process was repeated without the knowledge of drug ingestion, the patients thus being diagnosed "blind."

The clinical and laboratory features of these patients were then compared to those of patients presenting during the same period with three conditions that are particularly difficult to distinguish from drug jaundice⁸⁻⁹—namely, viral hepatitis, carcinoma of the extrahepatic biliary tree, or primary biliary cirrhosis.

Results

Of the 374 patients with jaundice assessed by the computer-assisted model there were 21 (5.6%) in whom a final diagnosis of drug hypersensitivity jaundice was made. In the previous computer program drug jaundice was classified on the basis of the drug taken, and was divided into "chlorpromazine jaundice" and "jaundice due to other drugs."⁴ It had been hoped that this would correspond to "cholestatic" and "hepatic" groups of patients, but in the present series there were four patients (who had received methyldopa or pyrazinamide) out of 21 who showed histological features on liver biopsy of acute inflammation,

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while the other 17 showed features of both cholestasis and inflammation. The mean serum aspartate aminotransferase (514 IU/l.) in the former group was significantly higher ($P < 0.001$) than that in the latter (86 IU/l.), but the mean serum alkaline phosphatase was not significantly different (20.4 and 31.0 K.A. U/100 ml respectively). There was no significant difference ($P > 0.1$) in the incidence of weight loss, abdominal pain, vomiting, pruritus, or loss of taste of smoking between the two groups. We did not, therefore, feel justified in separating patients with drug hypersensitivity jaundice into distinct "cholestatic" and "hepatic" groups and all patients have therefore been grouped together in this paper.

Apart from the four patients mentioned, 11 had received chlorpromazine, three chlordiazepoxide, one diazepam, one Norinyl-1 (an oral contraceptive containing norethisterone and mestranol), and one both ampicillin and oral tetracycline. Eleven of the 21 patients had been transferred from other hospitals because of difficulty in diagnosis. Four patients were jaundiced for over four months and one for 15 months. In one patient smooth muscle antibody was detected in the serum at a titre of 1/10, and in three antinuclear factor at a titre of 1/10. Serum antimitochondrial antibodies were not detected in any patient.

COMPUTER-ASSISTED DIAGNOSIS

When the information regarding drug exposure was left out drug jaundice was calculated as the most likely diagnosis in 17 patients (81%), of whom 11 had a probability of > 0.96 . In the four patients who were wrongly diagnosed the computed diagnoses were tumour of the extrahepatic biliary tree in three cases and viral hepatitis in one. In the 17 correctly diagnosed patients there were 14 different items of information that provided the greatest increase in the likelihood of drug hypersensitivity jaundice compared with the next most likely diagnosis. Only a low percentage of polymorphonuclear leucocytes (three patients) and a normal liver area measured by perimetry on the ^{99m}Tc liver scintiscan (two) did so in more than one patient.

When the history of drug ingestion was then included in the information entered in the computer, drug hypersensitivity jaundice was calculated to be the most likely of the 11 possible diagnoses in all 21 patients, of whom 17 had a probability of over 96% certain. The single item of information that provided the greatest increase in the probability of drug hypersensitivity jaundice while reducing that of the next most likely diagnosis varied from patient to patient. The history of drug ingestion did so in only 12 patients, a low polymorphonuclear leucocyte count in three, and other factors in the remaining six.

A history of drug ingestion did not necessarily mean that the model gave drug jaundice as the most likely diagnosis. Of 344 patients diagnosed by the model as having jaundice due to causes other than drugs there was a history of ingestion of potentially hepatotoxic drugs, such as chlorpromazine, chlordiazepoxide, and oral contraceptives in 64 (table I). Other features, such as the serum alkaline phosphatase or the presence of ascites, were more important in making the correct diagnosis in these patients. Nevertheless, the computer incorrectly diagnosed drug jaundice in four patients who were finally proved to have other conditions. Two of these gave a history of drug ingestion. Thus of 64 patients with non-drug jaundice, who had, however, given a positive drug history, 62 were correctly diagnosed as having jaundice due to a cause other than drugs.

In two patients the final diagnosis was found to be drug hypersensitivity jaundice after the model had suggested it, but before a drug history was obtained. In one the diagnosis was difficult because the clinical, laboratory, and histological features were inconclusive. The model, by making optimal use of all the data, diagnosed drug jaundice with a probability of > 0.96 . Because of this the history was retaken and a history of chlordiazepoxide ingestion finally elicited.

TABLE I—Patients with Jaundice due to Causes other than Drug Hypersensitivity who gave a History of Potentially Hepatotoxic Drug Ingestion

Disease	Positive Drug History	Total
Viral hepatitis	12	70
Fulminant hepatic failure	19	33
Active chronic hepatitis	1	30
Primary biliary cirrhosis	5	21
Alcoholic and cryptogenic cirrhosis	6	33
Tumour of biliary tree	12	95
Gall stones	5	37
Infiltration of liver by tumour	4	15
Gilbert's disease	0	10
Total	64	344

COMPARISON WITH OTHER DISEASES

The clinical and laboratory features of the 21 patients with drug hypersensitivity jaundice were compared to those in 70 patients with viral hepatitis, 21 patients with primary biliary cirrhosis, and 95 with tumour of the extrahepatic biliary tree (tables II and III). For discrete variables, such as the number of patients with abdominal pain, the χ^2 test with Yate's correction was used. No significant differences from drug hypersensitivity jaundice were shown for discrete variables (table II). For continuous variables, such as the serum bilirubin, the mean and standard deviation were calculated and Student's t test used, with logarithmic transformation where the variable had a log-normal distribution. The mean serum aspartate aminotransferase was significantly higher in patients with viral hepatitis and the mean length of history significantly longer in primary biliary cirrhosis, than in patients with drug hypersensitivity jaundice (table III).

TABLE II—Comparison between Certain Discrete Variables in Patients with Drug Hypersensitivity Jaundice, Viral Hepatitis, Primary Biliary Cirrhosis and Tumour of Extrahepatic Biliary Tree

	Percentage of Patients Exhibiting Symptom			
	Drug Hypersensitivity Jaundice	Viral Hepatitis	Primary Biliary Cirrhosis	Tumour of Biliary Tree
Weight loss	56	66	70	78
Abdominal discomfort or pain	15	43	9	37
Vomiting	55	68	25	48
Pruritus	90	62	78	73
Loss of desire for smoking	29	68	25	45

TABLE III—Comparison between Continuous Variables in Patients with Drug Hypersensitivity Jaundice, and Viral Hepatitis, Primary Biliary Cirrhosis, and Tumour of Extrahepatic Biliary Tree

	Drug Hypersensitivity Jaundice	Viral Hepatitis	Primary Biliary Cirrhosis	Tumour of Biliary Tree
Age*	53.3 (18.4)	35.4 (14.6)	53.5 (9.7)	60.2 (13.5)
Duration of history to time of diagnosis (weeks)†	4.8 (1.8)	4.6 (2.0)	56.2 (3.1)‡	10.4 (2.5)
Serum bilirubin (mg/100 ml.)*	11.3 (7.8)	11.3 (8.3)	9.8 (10.3)	14.8 (9.9)
Serum alkaline phosphatase (K.A. U/100 ml)†	22.9 (2.4)	20.4 (1.6)	67.3 (2.2)	56.3 (2.0)
Serum aspartate aminotransferase (IU/l.)†	121 (3.0)	323 (3.1)‡	123 (2.3)	86 (2.2)
Serum cholesterol (mg/100 ml)†	263 (1.2)	260 (1.3)	345 (1.7)	339 (1.5)
W.B.C./mm ³	7,480 (2,794)	7,535 (4,414)	7,877 (4,315)	9,885 (5,656)
Percent. polymorph count*	59.5 (53.3)	63.8 (14.2)	69.2 (14.0)	79.1 (11.3)
Percent. eosinophil count*	5.8 (4.0)	3.9 (3.9)	4.7 (4.6)	1.9 (3.0)
Liver area in cm ² on scintiscan*	184 (22)	239 (54)	241 (76)	253 (51)

*Mean ($\pm$ S.D.).

†Geometric mean (S.D.).

‡Significantly different ($P < 0.05$) from drug hypersensitivity jaundice.

There were also two patients who were finally proved to have primary biliary cirrhosis in whom cholestatic jaundice first developed after exposure to oral contraceptives. They became jaundiced two and 12 weeks after starting the drug and anti-mitochondrial antibodies were positive at the time of presentation. The histological appearances of liver biopsy specimens obtained at the time of presentation were those of early primary biliary cirrhosis. In one patient the computed diagnosis was primary biliary cirrhosis, with and without the drug history being included. In the other the computed diagnosis was drug jaundice when the drug history was included, and primary biliary cirrhosis when it was left out.

Discussion

Jick *et al.*¹⁰ reported from the United States that 4.8% of all drug exposures were associated with an adverse reaction, and 0.1% of these with hepatic failure, and Klatzkin¹¹ listed over 40 drugs marketed in the last 20 years that have caused liver injuries. In the present series, drug hypersensitivity was the sixth most common of 11 causes, being less frequent than viral hepatitis, fulminant hepatic failure, active chronic hepatitis, cirrhosis, tumour of the biliary tree, or gall stones.⁴ The patients may not be representative of drug jaundice in general since over half had been referred from other hospitals for diagnosis or treatment.

The difficulty of diagnosing drug hypersensitivity jaundice without a specific test, such as the lymphocyte transformation test¹² or deliberate¹³ or inadvertent¹⁴ re-challenge with the drug, is shown by the similarity of the clinical and biochemical features to those of jaundice from other causes. Johnson and Doenges⁸ emphasized the difficulty of differentiating cholestasis due to chlorpromazine from that due to extrahepatic biliary obstruction, and pointed out that diagnosis without resorting to operation is safer and more efficient, and Popper and Schaffner¹⁵ described it as a major diagnostic problem. In Werther and Korelitz's¹⁶ series of 22 patients with chlorpromazine jaundice 14 were initially incorrectly diagnosed and seven were needlessly subjected to laparotomy; percutaneous transhepatic cholangiography¹⁷ or endoscopic retrograde cholangiopancreatography¹⁸ may help in making the correct diagnosis. The performance of the computer-assisted model is satisfactory in correctly diagnosing all patients provided a drug history is obtained. When a drug history was not entered in the computer three patients were incorrectly diagnosed as having a tumour of the biliary tree. This emphasizes the importance of eliciting a full and detailed drug history in any patient with jaundice of obscure cause to avoid unnecessary investigation or operation. Nevertheless, when all the other available information points to a different cause of jaundice, the calculated diagnosis is not changed by a positive drug history alone.

Because the computer calculates probabilities using the prevalence of each item of information in its past experience of each disease, rather than using the physicians' general impressions, some surprising and unpredictable pieces of information proved

important in making a diagnosis of drug hypersensitivity jaundice. Even when a history of drug ingestion was included in the history, in nine patients it was a different piece of information that gave the greatest increase in the likelihood of drug jaundice above that of the second most likely diagnosis.

The relation between drug jaundice and primary biliary cirrhosis is interesting. In the two patients mentioned the drug history was probably coincidental, but patients with chronic chlorpromazine jaundice have been reported on whose clinical features were similar to primary biliary cirrhosis.¹⁹ Lewis and Arias²¹ reported on 18 patients in whom the Dubin-Johnson syndrome was found by oral contraceptives, and oral contraceptives may apparently reveal primary biliary cirrhosis.

Other workers²² separated drug jaundice into cholestatic and hepatitic groups. Though a few of our patients had a typical hepatitis-like syndrome and some predominant cholestasis, there was considerable overlap between the two groups on both clinical and histological criteria. With a larger series of patients such a distinction might have become apparent.

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