AN INTENSIVE DRUG MONITORING STUDY SUGGESTING POSSIBLE CLINICAL IRRELEVANCE OF IMPAIRED DRUG DISPOSITION IN LIVER DISEASE

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1 Liver disease can alter the disposition and clinical effects of drugs. However, even though altered drug disposition occurs, there is no clinical evidence relating it to an increased susceptibility to adverse drug reactions (ADRs).

2 An intensive prospective drug monitoring study of 2,582 hospitalized patients was conducted. The adverse drug reactions probability scale (APS) was used to assess ADRs. Only non-mild, definite or probable ADRs (APS ≥ 5) were included. Severity of liver dysfunction was assessed by a composite clinical and laboratory index (CCLI).

3 The frequency of ADRs was higher in 402 patients with cirrhosis (27.4%) than in 661 with renal dysfunction (22.8%) and in 249 with other parenchymatous liver diseases (13.7%) or in 1,270 patients with neither liver diseases nor renal dysfunction (10.9%) ($\chi^2_3 = 85.53$, $P < 0.001$). The frequency of ADRs in cirrhotics was highly correlated with the severity of the liver dysfunction measured by CCLI ($r = 0.82$, $P < 0.001$).

4 Drugs predominantly eliminated by liver metabolism were not among those most commonly inducing ADRs or those causing severe reactions in cirrhotics. Thus, frusemide caused the most common and the most severe ADRs, whereas reactions induced by sedatives were uncommon. Drug-induced hepatic encephalopathy was more common in cirrhotics receiving diuretics (13.3%) than in those receiving sedatives (1.8%) ($\chi^2_{y.c.} = 5.29$, $P < 0.025$). Patients with alcoholic liver disease had more drug-induced hepatic encephalopathy (7.7%) than those with non-alcoholic liver disease (1.2%) ($\chi^2_{y.c.} = 11.86$, $P < 0.001$).

5 These results indicate that susceptibility to ADRs is increased only in severe cirrhosis and that the most common and severe ADRs seem more likely related to enhanced pharmacodynamic action than to impaired drug disposition.

Introduction

Impaired liver function can alter drug disposition (Blaschke, 1977; Hoyumpa *et al.*, 1978; Roberts *et al.*, 1979a,b; McQueen, 1980; Williams & Mamelok, 1980) and cirrhosis of the liver is associated with an increased frequency of adverse drug reactions (ADRs) (Naranjo *et al.*, 1978a,c, 1979). However, despite the altered drug disposition, there is no clinical evidence indicating that the increase in susceptibility to ADRs in cirrhotics is related to abnormal metabolism. Information coming from previous studies on ADRs (Naranjo *et al.*, 1978a) is of somewhat limited clinical relevance because mild

reactions were included and no operational criterion for diagnosing ADRs was available at the time of the study. Furthermore, the relationship between the severity of the liver disease and the frequency of ADRs was not fully explored because no reliable index for assessing liver dysfunction using the combined information of clinical and laboratory data was available. Recently, these methodological problems have been solved. An operational method for assessing ADRs, the adverse drug reaction probability scale (APS), has been developed (Naranjo *et al.*, 1981), and a sensitive composite clinical and laboratory

index (CCLI) for assessing the severity of liver disease has been reported (Orrego *et al.*, 1979).

This study was undertaken to establish the frequency and determinants of ADRs in patients with cirrhosis and other parenchymatous liver diseases using the APS and CCLI. We also assessed whether drugs predominantly eliminated by liver metabolism were among those inducing the most severe and/or frequent ADRs. Finally, the relationship between severity of liver dysfunction (as determined by CCLI) and ADRs was further explored.

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Methods

The study was an intensive prospective drug monitoring study of 2,582 hospitalized patients admitted consecutively to monitored medical wards at the Jose Joaquin Aguirre Hospital in Santiago, Chile (90% of patients) and to the Addiction Research Foundation, Clinical Institute, Toronto, Canada (10% of patients). The 2,582 patients were stratified in four mutually exclusive disease categories: cirrhosis of the liver (402); other parenchymatous liver diseases (249); renal dysfunction (661); and neither liver disease nor renal dysfunction (1270). Patients with cirrhosis and functional renal impairment were included in the group with cirrhosis of the liver. Comparisons of frequencies and characteristics of ADRs were based on this classification. The patients were surveyed by a team of clinical pharmacologists and clinical pharmacists in accordance with procedures which have been previously described (Naranjo *et al.*, 1978a,b, 1979).

The following characteristics of each patient were recorded: name, sex, weight, height, duration of hospitalization, discharge diagnoses, previous history of ADRs, allergy and hepatic encephalopathy, liver function tests (direct and total bilirubin, glutamic-oxaloacetic and glutamic-pyruvic transaminase, prothrombin time, alkaline phosphatase, total protein, serum albumin), and renal function tests (blood urea nitrogen, serum creatinine, and creatinine clearance). When a drug was prescribed the pharmacist recorded the route of administration and reasons for the prescription (obtained from the attending physician). When the drug was discontinued, duration of treatment and total and daily dose were recorded. When an ADR was suspected, the following characteristics were analyzed: symptoms, signs, drug(s) probably implicated, mechanism, probability, severity, treatment, duration and outcome.

The following definitions were used:

Adverse drug reaction (ADR): Any noxious unintended, and undesired effect of a drug that occurs at doses usually administered in man for prophylaxis, diagnosis, or therapy. (This definition excludes therapeutic failures, intentional and accidental poisoning, and drug abuse). The severity of ADRs is classed as lethal, severe, moderate, or mild in accordance with criteria already established (Naranjo *et al.*, 1978b, 1979).

Mild: No antidote, therapy or prolongation of hospitalization is required.

Moderate: Requires a change in drug therapy although not necessarily discontinuation of the drug. It may prolong hospitalization and require specific treatment.

Severe: Potentially life-threatening, requires discontinuation of drug, specific treatment, and prolonged hospitalization.

Lethal: Directly or indirectly contributes to the death of the patient.

The probability that an adverse event is related to drug therapy was assessed using the adverse drug reaction probability scale (APS) (Naranjo *et al.*, 1981; Busto *et al.*, 1982). The APS is a short questionnaire (10 questions) which systematically analyzes the various components that must be assessed to establish the association between a drug and adverse event (i.e. pattern of response, temporal sequence, dechallenge, rechallenge, alternative causes, placebo response, drug levels in body fluids or tissues, dose-response relationship, previous patient experience with the drug and confirmation by objective evidence). Each question can be answered positive (yes), negative (no) or unknown or inapplicable (do not know), and is scored accordingly. The total score gives the probability that a certain drug caused the ADR. Scores range from -3 (a non-drug related event) to +12 (a definitely drug-related event). In this study only ADRs scoring ≥ 5 (i.e. definite or probable) were included (Naranjo *et al.*, 1981).

A quantitative estimate of the severity of liver disease was calculated for every patient using a composite clinical and laboratory index (CCLI). This scoring system is based on the concept that the severity of liver disease is proportional to the number of abnormal clinical and laboratory findings. The total combined score is obtained by adding the scores for the various clinical and laboratory abnormalities. The higher the score, the more severe the liver disease (Orrego *et al.*, 1979).

The diagnosis of cirrhosis of the liver was made by clinical and biochemical signs and in 58% of patients by liver biopsy. Hepatic encephalopathy was diagnosed when alterations in behaviour (ranging from lethargy to deep coma), asterix and fetor hepaticus were present. In addition, impaired problem solving or handwriting, and/or increased NH_3 level were commonly present (Leevy *et al.*, 1976). Since the aetiology of hepatic encephalopathy appears to be multi-factorial (Hoyumpa *et al.*, 1979), we have defined hepatic encephalopathy in a broad sense to include not only those cases associated with hyperammonaemia, but also those secondary to other cerebral insults such as sedatives. Blood urea nitrogen (BUN) above 25 mg/100 ml and/or creatinine clearance below 80 ml/min were the criteria for renal dysfunction. Admission biochemical tests were used for correlations. Data were analyzed at the Computer Services, Addiction Research Foundation, using the Statistical Analysis System (SAS) (The SAS Institute, 1979), and the Statistical Package for the Social Sciences (SPSS) (Nie *et al.*, 1979).

Results

Patient characteristics and frequency of ADRs by disease type

Table 1 summarizes the age, sex, number of drugs administered, duration of hospitalization and the

frequency of ADRs in the 2,582 patients stratified by disease type. This paper will focus on the results in cirrhotics and the findings of groups II and IV are only included for the purpose of comparison. A three-way analysis of the frequency table of disease type by sex by occurrence of adverse drug reactions (Table 1) was performed using a linear model (Grizzle *et al.*, 1969). This analysis showed that sex and disease type are major determinants of the frequency of ADRs. The cirrhotic patients had the highest percentage of ADRs (27.4%), followed by those with renal dysfunction (22.8%), those with other parenchymatous liver diseases (13.7%), and those with other diseases (10.9%) ($\chi^2_3 = 85.53$, $P < 0.0001$). Sex was also related to the probability of having an ADR since females had more ADRs than males regardless of their disease type ($\chi^2_1 = 31.35$, $P < 0.0001$). The interaction between sex and disease type was not statistically related to adverse reactions ($\chi^2_3 = 4.55$, NS). In all groups the number of drugs received was higher ($P < 0.001$) and the duration of hospitalization was longer ($P < 0.001$) in patients with ADRs. Differences in age were not statistically significant.

Manifestations of ADRs

Figure 1 shows that manifestations of ADRs varied according to the patient's disease. The results of groups II and IV are included for the purpose of comparison. Metabolic disturbances (predominantly electrolyte imbalances) were the most common

Table 1 Patients characteristics and frequency of adverse drug reactions (ADRs) by disease type – No. – (%)*

Disease type	Number of patients	Age (years) mean $\pm$ s.d.	Sex		Length of hospitalization (days) (mean $\pm$ s.d.)	Number of drugs administered (mean $\pm$ s.d.)
			M	F		
I Cirrhosis of the liver	402	51.4 $\pm$ 10.8	275	127	21.9 $\pm$ 15.8	7.0 $\pm$ 4.4
with ADRs	110(27.4)	51.7 $\pm$ 10.9	63(22.9)	47 (37.0)	31.2 $\pm$ 20.7	9.7 $\pm$ 4.9
without ADRs	292	51.3 $\pm$ 10.8	212(77.1)	80 (63.0)	18.5 $\pm$ 11.8	5.9 $\pm$ 3.6
II Renal dysfunction	661	44.3 $\pm$ 19.5	325	336	19.4 $\pm$ 14.1	6.8 $\pm$ 4.3
with ADRs	151(22.8)	43.3 $\pm$ 19.1	58(17.9)	93 (27.7)	26.9 $\pm$ 18.3	9.6 $\pm$ 5.0
without ADRs	510	44.6 $\pm$ 19.6	267(82.1)	243 (72.3)	17.2 $\pm$ 11.7	6.0 $\pm$ 3.8
III Other parenchymatous liver diseases	249	42.3 $\pm$ 17.8	113	136	18.4 $\pm$ 12.5	4.8 $\pm$ 3.4
with ADRs	34(13.7)	47.2 $\pm$ 17.9	8(7.1)	26 (19.1)	26.9 $\pm$ 14.7	8.7 $\pm$ 2.8
without ADRs	215	41.5 $\pm$ 17.7	105(92.9)	110 (80.0)	17.1 $\pm$ 11.6	4.2 $\pm$ 2.8
IV Neither liver disease nor renal dysfunction	1270	46.6 $\pm$ 18.7	578	690**	16.8 $\pm$ 11.5	5.0 $\pm$ 3.4
with ADRs	138(10.9)	46.9 $\pm$ 17.4	45(7.8)	93 (13.5)	23.4 $\pm$ 15.6	8.0 $\pm$ 4.1
without ADRs	1132	46.6 $\pm$ 18.9	533(92.2)	597 (86.5)	15.9 $\pm$ 10.7	4.6 $\pm$ 3.1
V All patients	2582	46.4 $\pm$ 18.0	1291	1289	18.4 $\pm$ 13.2	5.8 $\pm$ 3.9
with ADRs	433(16.8)	46.9 $\pm$ 16.9	174(13.5)	259 (20.1)	26.9 $\pm$ 18.1	9.0 $\pm$ 4.7
without ADRs	2149	46.3 $\pm$ 18.2	1117(86.5)	1030 (79.9)	16.7 $\pm$ 11.2	5.1 $\pm$ 3.4

*see text for statistical analyses

**missing data on two patients

Figure 1 Disease-related variations in manifestations of adverse drug reactions. See text for classification of disease categories.

ADRs observed in cirrhotics (61.3%). In contrast, digestive symptoms and skin problems were diagnosed more frequently in patients with other diseases. Central nervous system manifestations were also common in patients with liver diseases. These symptoms varied from mild reactions such as dizziness to severe ones such as hepatic encephalopathy. Twenty-five cases of hepatic encephalopathy were observed in cirrhotic patients (frusemide 21, hydrochlorothiazide 2, chlorthalidoxepoxide 1, chlorpromazine 1). Manifestations of ADRs in patients with other

diseases were similar to those previously reported (Naranjo *et al.*, 1978b; Ruiz *et al.*, 1978).

Drugs inducing ADRs in cirrhotics

In the cirrhotics, ADRs were most commonly associated with diuretics, parenteral solutions, potassium salts, antimicrobials and sedatives. Table 2 shows the drugs most commonly inducing ADRs in cirrhotics. Frusemide was one of the most commonly prescribed drugs and caused the highest rate of

Table 2 Drugs most commonly inducing adverse drug reactions in cirrhotics

Drugs	Patients receiving drug	Patients with adverse reactions	
		Number	(%)
<i>Diuretics</i>			
Frusemide	174	67	38.5
Triamterene	58	3	5.2
Spironolactone	55	5	9.1
Hydrochlorothiazide	27	5	18.5
<i>Intravenous solutions</i>			
Dextrose 10% in water	50	2	4.0
<i>Potassium salts</i>			
Potassium chloride	190	11	5.8
Potassium gluconate	94	2	2.1
<i>Antimicrobials</i>			
Neomycin sulphate	156	1	0.6
Penicillin G sodium	87	1	1.2
<i>Sedatives</i>			
Chlordiazepoxide	71	1	1.4
Diazepam	51	1	2.0
Chlorpromazine	22	2	9.1

Table 3 Adverse reactions to frusemide by disease type

Disease	Patients receiving drug	Patients with adverse reactions Number (%)
Liver cirrhosis	174	67 (38.5)
Other liver diseases	26	5 (19.2)
Renal dysfunction	315	35 (11.1)
Neither liver disease nor renal dysfunction	210	12 (5.7)
Total	725	119 (16.4)

$F_{3,721} = 32.36$, $P < 0.001$. See text for details on statistical analysis.

adverse reactions. The pattern of ADRs was similar to that previously described with the most common reactions being electrolyte disturbances, volume depletion and hepatic coma (Naranjo *et al.*, 1979). There was a clear disease-related variation in the frequency of adverse reactions to frusemide (Table 3). The gradient was as follows: cirrhotics (38.5% of patients) > other liver diseases (19.2%) > renal dysfunction (11.1%) > neither liver disease nor renal dysfunction (5.7%) ($F_{3,721} = 32.36$, $P < 0.001$). In each disease category the patients with adverse reactions received significantly higher total doses of frusemide than those without adverse reactions ($F_{1,720} = 5.13$, $P < 0.05$). However, the total dose of frusemide accounts for a very small proportion of the variation in adverse reactions (0.6% as opposed to 12.2% of the variation accounted for by disease type). The interactions between total frusemide dose and disease type are all non-significant in predicting the occurrence of adverse reactions (cirrhosis $\times$ total dose: $F_{1,717} = 0.94$ NS; other liver diseases $\times$ total dose: $F_{1,717} = 1.12$, NS; renal dysfunction $\times$ total dose: $F_{1,717} = 0.83$ NS). Thus, the major determinant of adverse reactions to frusemide is the disease type. Even though sedatives were commonly prescribed to cirrhotics, the frequency of ADRs was low. Particularly important is that the frequency of drug-induced hepatic encephalopathy was significantly higher in cirrhotics receiving diuretics (13.3%) than in those receiving sedatives (1.8%) ($\chi^2_{y.c.} = 5.29$, $P < 0.025$) (Table 4). In addition, patients with alcoholic liver disease had more drug-induced hepatic encephalopathy (7.7%) than those with non-alcoholic liver disease (1.2%) ($\chi^2_{y.c.} = 11.86$, $P < 0.001$). The drugs most commonly inducing ADRs in patients with other diseases did not differ from previous reports (Naranjo *et al.*, 1978b; Ruiz *et al.*, 1978).

Severity of liver dysfunction in cirrhotics and ADRs

The Composite Clinical and Laboratory Index (CCLI) gives a quantitative estimate of the severity of the

Table 4 Frequency of drug-induced hepatic encephalopathy in cirrhotics treated with diuretics or sedatives*

Drugs	Patients receiving drug during hospitalization	Patients with hepatic encephalopathy Number (%)
Diuretics**	150	20 (13.3)
Sedatives***	56	1 (1.8)

$\chi^2_{y.c.} = 5.29$, d.f. = 1, $P < 0.025$

*only patients who exclusively received either diuretics or sedatives are included in this table

**frusemide or hydrochlorothiazide

***chlordiazepoxide or chlorpromazine

liver disease. Figure 2 shows that increases in CCLI and in the frequency of ADRs were highly correlated ($r = 0.82$, $P < 0.001$) in the cirrhotics. The results on cirrhotics receiving frusemide demonstrate the influence of the severity of liver dysfunction on the development of adverse drug reactions. Frusemide is the drug most commonly inducing ADRs in cirrhotics, and the frequency of adverse reactions correlated with CCLI ($r = 0.78$, $P < 0.001$). Furthermore, since a previous study indicated that the frequency of adverse reactions to frusemide in cirrhotics depends on both total frusemide dose and severity of liver dysfunction (Naranjo *et al.*, 1979), we studied this interaction. Figure 3 shows the tri-dimensional relationship between CCLI, total frusemide dose and number of cases with adverse reactions. A multiple regression analysis of these data indicates that the occurrence of adverse reactions is significantly related to CCLI ($F_{1,165} = 9.82$, $P < 0.005$), but does not depend on total dose ($F_{1,165} = 0.04$, NS), or on interaction between CCLI and total dose ($F_{1,165} = 0.04$, NS). These results indicate that the severity of liver dysfunction (CCLI) is the major determinant of adverse reactions to frusemide.

Discussion

This study confirmed that not all patients with liver disease, but only those with liver cirrhosis are more susceptible to develop adverse drug reactions (ADRs). Using strict criteria for assessing ADRs, it was possible to show that the increased frequency of ADRs was mostly related to the severity of the liver dysfunction. In addition, drugs predominantly eliminated by liver metabolism were not among those most commonly inducing ADRs or those causing the most severe reactions. These findings have several important implications.

A major problem in drug monitoring studies is the lack of reliable method of assessing the causal relationship between drugs and adverse events. Such a

Figure 2 Positive correlation between a composite clinical and laboratory index (CCLI) measuring severity of liver disease and the frequency of adverse drug reactions in patients with cirrhosis of the liver.

method is needed because the incidence of adverse events should be estimated only from cases identified as definite or probable ADRs (Naranjo *et al.*, 1981). Recent studies have shown that the Adverse Drug Reactions Probability Scale (APS) is a valid and reliable method for assessing ADRs (Naranjo *et al.*, 1981; Busto *et al.*, 1982). Some argue that the operational definitions of ADRs are time consuming and, therefore, they would have little application in large scale studies involving thousands of cases. This report demonstrates the feasibility of conducting drug monitoring studies in which the APS was systematically applied to a large sample of patients for obtaining reliable results. Thus, the APS or similar procedures should be used in future studies for improving quality of data when assessing the frequency and determinants of ADRs (Naranjo *et al.*, 1981; Busto *et al.*, 1982). The new estimate that 27.4% of cirrhotics develop ADRs while in hospital is possibly more accurate than the figure of 38.4% reported in a previous study (Naranjo *et al.*, 1978a), because this time only non-mild reactions considered definite or probable using the APS were included.

The susceptibility to ADRs is strongly related to the severity of the liver dysfunction. This is demon-

strated by the positive correlations between the CCLI and the overall frequency of ADRs, and the frequency of frusemide-induced adverse reactions. As clearly illustrated in the case of frusemide, our results indicate that even though the total dose of frusemide may be important, the major determinant of adverse reactions in cirrhotics is the degree of severity of the liver dysfunction (Figure 3). In addition, cirrhotics are more susceptible than patients with other diseases to frusemide-induced adverse reactions. These results are consistent with our previous findings (Naranjo *et al.*, 1978a, 1979). Therefore the use of frusemide should be carefully monitored in patients with severe liver dysfunction.

From a practical point of view, our findings indicate the need for special caution when some drugs are used in cirrhotics. Most of the reactions detected were associated with diuretics such as frusemide and consisted mainly of electrolyte disturbances, volume depletion and hepatic encephalopathy, which confirms our previous findings (Naranjo *et al.*, 1978a, 1979). A very important finding is that drug-induced hepatic encephalopathy was more common in cirrhotics receiving frusemide or hydrochlorothiazide than in those receiving sedatives. This contradicts the

Figure 3 Tri-dimensional relationship between the severity of liver disease (CCLI), the total dose of frusemide and the number of cases with adverse reactions in patients with cirrhosis of the liver receiving frusemide. See text for statistical analysis. ■ had ADR, □ no ADR.

assumption that the administration to cirrhotics of drugs for which the metabolism is impaired, is associated with more common or more severe toxicity (Hoyumpa *et al.*, 1978). In fact, frusemide, the drug most commonly inducing hepatic encephalopathy and other adverse reactions, is mainly excreted unchanged by the kidney (Benet, 1979). Altered disposition does not seem to play an important role on frusemide toxicity in cirrhotics. For example, studies on frusemide disposition are contradictory. Some indicate impairment of frusemide elimination (Fuller *et al.*, 1981; Sawhney *et al.*, 1981) whereas others have found no change (Allgulander *et al.*, 1980; Keller *et al.*, 1981; Verbeeck *et al.*, 1982). More importantly, none of these studies have shown a clinically important reduction in frusemide clearance. In spite of the discrepancy in findings, there is agreement that differences in disposition play little role, if any, in the clinical effect of frusemide in cirrhotics (Sawhney *et al.*, 1981; Verbeeck *et al.*, 1982). Our findings are consistent with this view.

Drugs predominantly eliminated by liver metabolism were not among those most commonly inducing ADRs or those causing the most severe reactions. This suggests that variations in pharmacodynamics might be a more important determinant of clinical drug toxicity in cirrhotics. Our findings that patients with alcoholic liver disease had more drug-induced hepatic encephalopathy than those with non-alcoholic liver disease might reflect such enhanced sensitivity to various kinds of cerebral insults such as the psychoactive drug itself or the increased ammonia

associated with diuretic-induced hepatic coma (Hoyumpa *et al.*, 1979). The increased susceptibility to drug-induced hepatic encephalopathy could be related to the cerebral atrophy described in chronic alcoholics (Carlen *et al.*, 1981). In fact, the toxicity of some drugs (e.g. sedatives) in cirrhotics has been related to enhanced receptor sensitivity (Hoyumpa *et al.*, 1978). Accordingly, some pharmacodynamic studies suggest that the cerebral sensitivity to some drugs such as morphine (Laidlaw *et al.*, 1961), chlorpromazine (Maxwell *et al.*, 1972) and diazepam (Branch *et al.*, 1976) might be enhanced in these patients. However, further experimental studies to elucidate the precise mechanism of this phenomenon are required.

In conclusion, the clinical relevance of studies showing impaired drug disposition in cirrhosis is unclear. Our study suggests that pharmacokinetic disturbances reported in cirrhotics are not always associated with clinically important drug toxicity. Our findings emphasize the need to correlate pharmacokinetic and pharmacodynamic findings (Gross, 1978). It is important to remark, however, that our findings are only applicable to those drugs most commonly prescribed in our patients. Further pharmacodynamic and drug monitoring studies for assessing the clinical relevance of variations in pharmacokinetics in cirrhosis and other diseases are mandatory.

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