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Computed Tomography of the Brain, Hepatotoxic Drugs and High Alcohol Consumption in Male Alcoholic Patients and a Random Sample from the General Male Population

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ABSTRACT

Computed tomography (CT) of the brain was performed in a random sample of a total of 195 men and 211 male alcoholic patients admitted for the first time during a period of two years from the same geographically limited area of Greater Stockholm as the sample. The same medical, social and neuroradiological methods were used for examination of the alcoholic inpatients as for the random controls. Laboratory tests were performed, including liver and pancreatic tests. Toxicological screening was performed and the consumption of hepatotoxic drugs was also investigated and the following were the types of drugs used: antiarrhythmics, antiepileptics, antiphlogistics, mixed analgesics, barbiturates, sulphonamides, benzodiazepines, clomethiazole and phenothiazine derivatives, all of which are metabolised by the liver. The group of male alcoholic inpatients and the random sample were then subdivided with respect to alcohol consumption and use of hepatotoxic drugs: Group IA, men from the random sample with low or moderate alcohol consumption and no use of hepatotoxic drugs; IB, men from the random sample with low or moderate alcohol consumption with use of hepatotoxic drugs; IIA, alcoholic inpatients with use of alcohol and no drugs; and IIB, alcoholic inpatients with use of alcohol and drugs.

Group IIB was found to have a higher incidence of cortical and subcortical changes than group IA. Group IB had a higher incidence of subcortical changes than group IA, and they differed only in drug use. Groups IIB and IIA only differed in drug use, and IIB had a higher incidence of brain damage except for anterior horn index and wide cerebellar sulci indicating vermian atrophy.

Significantly higher serum (S) levels of bilirubin, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (ASAT), alanine amino-transferase (ALAT), creatine kinase (CK), lactate dehydrogenase (LD) and amylase were found in IIB.

The results indicate that drug use influences the incidence of cortical and subcortical aberrations, except anterior horn index. It is concluded that the groups with alcohol abuse who used hepatotoxic drugs showed a picture of cortical changes (wide transport sulci and clear-cut or high-grade cortical changes) and also of subcortical aberrations, expressed as an increased widening of the third ventricle.

INTRODUCTION

In recent years, there have been a large number of computed tomography (CT) studies (2-4,7-9,12,13,15,17,19,23,25-27,29,31) of the morphological changes in the alcoholic brain. In these reports, the criteria for diagnosing alcoholism have varied widely. Some researchers have focused on heavy social drinkers (3,7-9) and there are reports based on Zimberg´s scale (23), the criteria of the National Council on Alcoholism (17), or special diagnostic criteria which were quantitatively determined, one, for example, being an intake of more than 50 g of ethanol per day (19). Others have excluded cases of delirium tremens, withdrawal seizure or Korsakoff´s syndrome from their studies (7,8). Background factors, including sex , age, duration of alcohol drinking or complications, also vary from report to report; only male patients were studied in some reports (2-4,19,29) while a few females were included in others (7-9,12,13,23,27). The criteria for exclusion of complications such as epilepsy, drug dependence other than alcoholism, head injury, intracranial hematoma, severe liver dysfunction and hepatocerebral syndrome differ among the reports.

Some authors have tried to assess the cerebral morphological status among persons without alcohol problems by comparison with various control groups. However, it is clear from the selection criteria of the groups that they cannot be considered representative of a general population.

Benzodiazepine users, as a group, have been found to have larger ventricle/brain ratios than controls but smaller than those of alcoholics (18). In a 6-year follow-up of 50 patients with primary dependence on sedative and hypnotic drugs, 26 patients (52%) were abusing drugs and/or alcohol at the time of follow-up. CT of the brain was performed in 33 of these 50 patients, and in 17 patients, 10 of whom were currently abusing drugs, there were indications of cortical atrophy (1). Rumbaugh et al. (30) reported on 6 drug abusers with dilatation of the ventricles and subarachnoid spaces, suggesting that cerebral atrophy can be related to drug abuse.

Caballeria et al. (6) found that systemic effects of alcohol may be exacerbated in patients receiving cimetidine and Leo et al. (20) found that hepatic cytosolic retinal dehydrogenase activity was increased 8-fold after phenobarbitone and ethanol administration, but no extrahepatic induction was observed.

The purpose of the present interdisciplinary study was to compare a random sample of men from the general population with alcoholic inpatients with regard not only to the incidence and location of morphological cerebral changes but also to the laboratory findings in relation to drinking habits and to the use of hepatotoxic drugs in combination with alcohol intake.

A special feature of this study is that the same instrument has been applied in different populations.

MATERIAL AND METHODS

The study comprised a sample from the general population and alcoholic inpatients consisting of men living in the catchment area of the Karolinska Hospital, a geographically limited area in the northern part of Stockholm (Solna and Sundbyberg) with about 80,000 inhabitants. The sample was drawn randomly from the National Register covering all Swedish inhabitants. The sample was stratified with regard to age and it was intended that a sample of 200 men should be drawn, with 40 in each of the age-groups 20-29, 30-39, 40-49, 50-59 and 60-65 years, in order to achieve the same degree of precision for all age-groups in the estimation of different variables.

The initial random sample drawn consisted of 209 men aged 20-65 years. Of this sample, 2 persons had died, 5 had moved more than 20 miles away from Stockholm, and 10 were living permanently abroad at the time of investigation and were thus excluded from the study. Nine persons refused to be examined and 2 refused to take part in the CT investigations. Thus, of the initial sample of 209 men, 181 were available for investigation. To increase the sample to 200, a supplementary sample of 19 men was drawn in exactly the same way as before, and all these men were available for investigation. The non-participant group was small and the drop-outs (11%) did not differ from the examined persons with respect to social status, age, education, civil status, employment status or data from official registers ($p>0.05$). Five men refused to undergo CT examination of the brain, and CT scans for a total of 195 men were therefore available.

The patient group comprised 211 men consecutively admitted to the Magnus Huss Clinic for alcohol diseases at the Karolinska Hospital. All were born on an uneven date and were staying at the clinic for at least one week for voluntary treatment. All alcoholic patients admitted for the first time during a period of 2 years from the same geographically limited area as the sample were investigated. The same medical, social and neuroradiological methods were used for examination of the 211 alcoholic inpatients as for the 195 random controls. Laboratory tests were performed, including liver and pancreatic tests. Blood samples were drawn in the morning after an overnight fast in the random sample and in the alcoholic inpatient group. Toxicological screening with the following assays was performed: serum concentrations of barbiturates, other sedatives and alcohol and urinary concentrations of meprobamate, benzodiazepines, alkaloids, phenothiazines, tricyclic antidepressants, amines stimulating the nervous system and salicylic acid. The amount of alcohol consumed, indications of alcohol dependence and alcohol-related complications were thoroughly assessed by means of a standardised procedure combining a self-administered questionnaire and a check-up interview. Two measures of alcohol consumption were used - the amount of alcohol consumed in the previous week in grams of absolute alcohol per day and the typical peak consumption in the last six months in grams of pure alcohol per day. The consumption in the last week was recorded, as it was considered that the subjects´ recall would be poorer for the period further back in time.

The drug consumption case history is composed of two parts. The first part focuses on drugs consumed during the last 24 months before admission and all prescription for the patient, data on type of drug and prescribing doctor. Drugs are coded in accordance with the Swedish

pharmacological register (FASS). The second part consists of a medicine chart/questionnaire with special emphasis on psychotropic and addictive drugs, and the consumption of hepatotoxic drugs was also investigated. The following were the types of drugs used: antiarrhythmic agents, antiepileptic agents, antiphlogistics, mixed analgesics, barbiturates, benzodiazepines, phenothiazine derivatives, sulphamethizole and sulphamethoxypyridazine derivatives and clomethiazole, all of which are metabolised by the liver (Table 1). This latter part of the drug consumption history is designed for the patient's own completion. Patients are asked to record the drugs which they are either using at present or have used during the last 24 months. Altogether 180 different drugs are itemised.

Table 1. Use of hepatototoxic drugs combined with alcohol consumption in the two groups IB and IIB. Pharmacological groups and the doses of each drug in grams per day (g/d) after the generic name. Minimum time of drug consumption in months for each drug group.

Pharmacological groups and the doses in g/d	Group IB: Random sample Low alcohol + drugs (n=31)	Duration of drug consumption in months	Group IIB: Alcoholic inpatients + drugs (n=40)	Duration of drug consumption in months
Antiarrhytmic drugs quinidine bisulph. 0.4; verapamil hydrochlor. 0.32	5	24	1	24
Antiepileptics Phenytoin sod. 0.4	5	24	0	0
Antiphlogistics ibuprofen 1.2	4	24	0	0
Mixed analgesics Dolerone 2 tablets/day	3	24	4	24
Barbiturates amylobarbitone 0.2; hexapropymate 0.4	2	24	10	24
Benzodiazepines nitrazepam 0.01; diazepam 0.02; chlordiazepoxide 0.03; oxazepam 0.03	7	24	10	24
Phenothiazine derivatives promethazine 0.05; chlorprothixene 0.05; alimemazine 0.08	3	24	8	24
Sulphamethizole 0.4 g, sulphamethoxypyridazine 0.1 g Sulfapral 4 tablets/day	2	1	0	0
Clomethiazole Hemineurin 0.9	0	0	7	6
N	31		40	

The validity of the drug consumption case history may be open to question. On the other hand, with regard to psychotropic drugs, many of the patients have shown an impressive knowledge of the names, doses and effects of the various drugs.

The group of male alcoholic inpatients and the random sample were then subdivided with respect to alcohol consumption and use of hepatotoxic drugs:

- (IA) men from the random sample with low or moderate alcohol consumption and no use of drugs (n=164);
- (IB) men from the random sample with low or moderate alcohol consumption with use of drugs (n=31);
- (IIA) alcoholic inpatients with use of alcohol but no drugs (n=171);
- (IIB) alcoholic inpatients with use of alcohol and drugs (n=40);

Computed tomography

The tomographic images were evaluated with regard to ventricular, cortical and cerebellar changes. An anterior horn index, i.e. Evan´ s ratio, was obtained by dividing the width of the anterior horns by the largest inner skull diameter. Values exceeding 0.31 were considered pathological.

A transverse diameter of the third ventricle exceeding 6 mm was also considered pathological. A four-step scale of degenerative cortical changes was used, based on a general assessment of the tomographs by the radiologist with regard to observations of widened sulci. In this scale, 1=normal, i.e. no sulci visible or sulci less than 3 mm in natural size, 2=suspected degenerative changes, i.e. up to 5 sulci exceeding 3 mm in diameter, 3= clear-cut changes, i.e. more than 5 sulci exceeding 3 mm in diameter and appearing in at least 2 cuts, and 4=high-grade changes, i.e. marked widening of a large number of sulci in all lobes. The inter-rater reliability of the scale has been found to be 0.81 (11).

RESULTS

Groups IA-IIB

Characteristics of the 2 groups of alcoholic inpatients and the 2 groups from the random sample who used and did not use drugs are presented in Table 2. The 40 alcoholic inpatients and drug-users in group IIB were significantly heavier. Ethanol was present in the blood in 2% of the random sample using no drugs, and in 10% of those using drugs, who had consumed 32 g and 49 g of alcohol per day respectively in the last week before examination in the hospital. Ethanol was present in the blood in 42% and 40% respectively of the inpatients not using and using drugs, who had consumed 250 g and 251 g per day respectively in the last week before admission to hospital. There were significantly more smokers in the 3 groups IB, IIA and IIB.

Twelve per cent of the sample who did not use drugs (group IA) and 19% of those who used drugs (group IB) were registered by the Temperance Board. Among the alcoholic inpatients who did not use drugs (group IIA) and those who used drugs (group IIB), 66% were registered by the Temperance Board.

Table 2. Characteristics of the 4 groups of men with different drinking habits with and without the use of hepatotoxic drugs.

	GROUP IA Random sample Low alcohol - no drugs (n=164)	GROUP IB Random sample Low alcohol + drugs (n=31)	GROUP IIA Alcoholic inpatients - no drugs (n=171)	GROUP IIB Alcoholic inpatients + drugs (n=40)
Age (years)	44±14	47±13	44±14	45±13
Alcohol intake previous week in g absolute alcohol/day	32±51	49±88	250±115****	251±126****
Registered by the Temperance Board (%)	12	19	66****	66****
Smokers (%)	44	58****	74****	80****
Alcohol in blood on arrival at hospital (%)	2	10 *	42****	40****

Degrees of significance in comparison with low alcohol-no drugs group by Student's t-test and Chi-square test. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

Liver and pancreatic tests

The results of alcohol-related liver and pancreatic tests in the subgroups are presented in Table 3. Significantly higher serum levels of bilirubin, GGT, ASAT, ALAT, CK, LD and amylase were found in the alcoholic group using drugs (group IIB) than in the other groups. In group IIA, with a high alcohol consumption and no drug use, only serum alkaline phosphatase (ALP), GGT, ASAT, ALAT and amylase were elevated. In group IB, the men from the random sample using drugs, significantly higher values of serum ALP, GGT and LD were found, but these values lay within the given reference ranges, except GGT.

In the men from the random sample who used drugs combined with alcohol (group IB), the drugs taken included antiarrhythmic agents (quinidine, verapamil), antiepileptics (Epanutin), antiphlogistics (Ibuprofen) dextropropoxyphene (Doleron) and benzodiazepine derivatives, all of which can cause increases in liver enzymes such as serum GGT, ASAT, ALAT and LD (see Table 1,3). Seventy per cent of the random sample using drugs (group IB) had pathological GGT values and 60% pathological values of ALAT. The most important of these drugs are anticoagulants, antiepileptic agents and barbiturates (10,16).

The drug profile of the 40 patients in group IIB and the men in group IB is shown in Table 1. None of the subjects used cardiovascular drugs such as digitalis, antihyperlipidemics, antidiabetics, or uricosuric drugs. The most frequently used non-psychotropic group of drugs was antacids. With regard to psychotropic drugs in group IIB, 25% of the subjects had experience of amylobarbitone and hexapropymate, and 26% of benzodiazepines like diazepam (Table 1). As regards non-addictive psychotropic drugs, 19% of the men reported using phenothiazine derivatives and 17% used clomethiazole, which is a drug usually prescribed for alcoholic abstinence.

Table 3. Alcohol-related liver and pancreatic disturbances in the 4 groups as reflected by mean values of serum bilirubin, ALP, GGT, ASAT, ALAT, CK, LD and amylase. Reference values in parenthesis.

	GROUP IA Random sample Low alcohol - no drugs (n=164)	GROUP IB Random sample Low alcohol + drugs (n=31)	GROUP IIA Alcoholic inpatients - no drugs (n=171)	GROUP IIB Alcoholic inpatients + drugs (n=40)
S-bilirubin (4-21 umol/l)	11±7	9±4	12±7	16±12 ***
S-ALP (0.8-4.0 ukat/l)	2.9±0.9	3.3±1.0 *	4.9±7.8 ***	4.3±2.0 ****
S-GGT (<1.00 ukat/l)	0.52±0.42	1.21±1.14 ****	4.40±8.21****	6.94±9.76 ****
S-ASAT (<0.70 ukat/l)	0.42±0.33	0.44±0.22	1.26±1.01****	2.26±1.91 ****
S-ALAT (<0.70 ukat/l)	0.42±0.42	0.46±0.26	1.15±0.91****	1.66±1.38 ****
S-CK (0.6-2.7 ukat/l)	2.4±1.7	3.0±4.3	2.3±2.1	3.4±5.0 *
S-LD (2.7-6.4 ukat/l)	5.6±0.9	6.2±2.1 **	7.3±1.8	8.2±2.1****
S-Amylase (1.1-5.0 ukat/l)	3.3±1.6	2.8±0.8	3.8±1.9 **	6.4±8.8 ****

Significance levels tested in comparison with group IA by Student's t-test and Chi-square test.
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

CT findings in groups IA-IIB

Cortical changes were found in 80% of group IIB(p<0.0001 compared with group IA) and 62% of group IIA(p<0.0001), and wide transport sulci in 28%(p<0.0001) of group IIB and 22% (p<0.0001) of group IIA. Users of hepatotoxic drugs had a higher incidence of cortical changes than non-users in groups IA and IIA vs IB and IIB respectively (Table 4).

In group IIA, 40% ($p<0.0001$) had a pathological anterior horn index, but in the groups that used drugs only 32-33% ($p<0.05$) had a pathological anterior horn index. The incidence of an enlarged third ventricle varied from 32 to 53% in the drug-using groups and was 35% in group IIA. Wide cerebellar sulci indicating vermian atrophy were observed in 35% of the men in groups IIB and IIA ($p<0.0001$) but were found in only 6% of group IB and 1% of group IA (Table 4).

Table 4. CT variables used in the 4 groups with different drinking habits with and without the use of hepatotoxic drugs.

CT measures	GROUP IA Random sample Low alcohol - no drugs (n=164) %	GROUP IB Random sample Low alcohol + drugs (n=31) %	GROUP IIA Alcoholic inpatients - no drugs (n=171) %	GROUP IIB Alcoholic inpatients + drugs (n=40) %
Cortical				
Wide transport sulci	4	10	22****	28****
Cortical changes (subjective rating: clear-cut or high-grade)	14	26	62****	80****
Subcortical				
Anterior horn index > 0.31	16	32*	40****	33*
Width 3rd ventricle > 6 mm	9	32****	35****	53****
Vermian atrophy	1	6	35****	35****

Degrees of significance tested in comparison with low alcohol-no drugs group by Chi-square test. *$p<0.05$; **$p<0.01$; ***$p<0.001$; ****$p<0.0001$.

DISCUSSION

Regarding potential bias, the CT images were assessed by 2 radiologists independently and the assessments were made blindly, i.e. without the radiologists' having any knowledge of the alcohol consumption of the patient in question. The study was performed on a representative sample of men from Greater Stockholm, and the sample was completely unselected, randomly chosen and age-stratified, and drawn by Statistics Sweden, a government agency.

The subjects knew that they were to undergo a health examination, and even though they may have consumed some alcohol the day before, they had not taken any on the day they came to the hospital. Blood samples were drawn in the morning after an overnight fast in the random sample and in the alcoholic inpatient group. None of the subjects was drunk at the time of the tests or had cerebral oedema according to the CT findings. They were thoroughly assessed concerning the amount of alcohol consumed, indications of alcohol dependence and alcohol-related complications,

by means of a standardised procedure combining a self-administered questionnaire and a structured interview. In exactly the same way as with alcoholic inpatients (24), a sample of 40 was selected randomly from the 200 men who answered the questions concerning alcohol habits. These men were asked to answer the same questions 6-24 months after the first occasion, and a test-retest analysis was performed using Spearman´s rank-order correlation and Kendall´s tau-b. Kappa does not utilise the ordinal information of the variable, and we therefore used Kendall´s tau-b with values between 0.56 and 1.00.

The methods used in the assessment of the CT images of the brain are well known and have been well documented for several years (3,4,25,26). At the Magnus Huss Clinic of the Karolinska Hospital, the same methods have been used for these purposes since 1976, both in alcoholics and in healthy control persons, with each subject assessed blindly by two examiners. The reliability has been ≥ 0.81 (11). In consideration of the above, there should be no important sources of bias regarding the population sample and the alcoholic inpatients or the CT examinations of the brain.

The drugs used are known to be metabolised by the liver and the findings in the subjects with combined drug abuse and alcoholism show the clinical importance of alcohol and drug interactions. Many of the central nervous effects of various drugs are potentiated by simultaneous intake of alcohol, and the elimination rates of many drugs are influenced both by chronic alcohol consumption and by possible liver damage (21).

Lader et al. (18) performed CT scanning in 20 patients who had taken benzodiazepines for a long period. The mean ventricular/brain area as measured by planimetry was larger than the mean values in an age and sex-matched group of control subjects, but was smaller than that in a group of alcoholics. There was no significant correlation between the CT findings and the duration of benzodiazepine therapy.

The present findings are in accordance with reports in the literature concerning cerebral changes on CT and the effects of combination of alcohol and drugs, namely that simultaneous alcohol and drug intake has an additive action on the central nervous system. Bergman (5) found that alcoholic patients had poorer results in neuropsychological tests and that these were related to CT changes. In Bergman´s study, the subjects in the alcoholic group were severely alcoholic, whereas our heavy drinkers from the random sample of the male population of Greater Stockholm were not social outcasts but had a high alcohol consumption. From the purely CT aspect, they resembled the social outcasts in Bergman´s study, the difference being that they drank smaller quantities of alcohol but used drugs at the same time.

Hernandez-Munoz et al. (14) found two types of alcohol dehydrogenase isoenzymes (differing in their affinity for ethanol, sensitivity to 4-methylpyrazole, and electrophoretic migration) in the human stomach. At the high ethanol concentrations prevailing in the gastric lumen during alcohol consumption, the sum of their activities could account for significant oxidation of ethanol. In vivo, therapeutic doses of cimetidine (but not famotidine) increased blood ethanol levels when ethanol was given orally but not when it was given intravenously, indicating a significant contribution of the gastric ADH to the bioavailability and thereby the potential toxicity of ethanol.

Roine et al. (28) found that aspirin may increase the bioavailability of ingested ethanol in humans, possibly by reducing ethanol oxidation by gastric alcohol dehydrogenase. Lieber (22) says that until recently it was commonly believed that the primary pathway for hepatic ethanol metabolism is due almost exclusively to the activity of cytosolic alcohol dehydrogenase, with a minor contribution from peroxisomal catalase. It is now recognised, however, that liver microsomes (through MEOS) participate in ethanol metabolism.

Caballeria et al.(6) found that the areas under the curve of blood ethanol concentrations after oral alcohol intake were twice as large with cimetidine as without. The results indicate that gastric alcohol dehydrogenase activity partly governs the systemic bioavailability of ethanol. Consequently, systemic effects of alcohol may be exacerbated in patients receiving cimetidine, which is metabolised by the liver.

The same instrument has been applied in different populations in this study and the most interesting and new finding seems to be the differences in levels of markers between drug-users and non drug-users. The pathological values often found in alcoholics could to a large extent be ascribed to concomitant drug use. That alcohol and drugs can interact and that the combination may be dangerous is well known. The importance of this in relation to the use of biomedical markers as screening instruments has probably not received sufficient attention.

In the present study, the greatest cortical and subcortical changes were found in the men of the small group IIB, who both had a high alcohol consumption and used drugs daily, but an exception was the anterior horn index, where group IIA, with high alcohol intake and no drug use, had a pathological index in 40%. In the random sample, the greatest cortical and subcortical changes were found in the men of the small group IB, who both had a relatively high alcohol consumption and used drugs daily. What we have found is that high alcohol consumption and drug use does not influence the anterior horn index so much as the other measures of brain damage.

From a purely scientific viewpoint, this means that even though there may be major CT changes in some patients, the use of alcohol in combination with drugs is the most important factor which gives pathological cortical and subcortical changes in the population and influences the changes in the alcoholic inpatient groups.

It is concluded that the alcoholic inpatients and the men in the random sample who use alcohol in combination with drugs are at greater risk and have more pathological CT scan items except the anterior horn index and also have more pathological liver and pancreatic tests, which has not previously been shown in the literature.

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