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Does liquor utilization surge the danger of extreme antagonistic occasions to ivermectin treatment?

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Abstract

The present investigation is a case-control study designed to assess the level of association between alcohol consumption and the occurrence of severe adverse reaction (SAE) following ivermectin consumption. Thirty-six (36) cases of SAE occurred in the health districts of Bankim, Nanga Eboko, Obala, Okola and Sa'a. Case and control (43) individuals were submitted to a questionnaire related to their alcohol consumption 24 before and 24 to 48 h following ivermectin intake. An in-depth interview of siblings and local health worker was conducted to assess alcohol consumption around Mectizan intake. The degree of alcohol use was assessed using the level of serum transaminases and the alcohol use disorder identification test (AUDIT). The alcoholic beverages of the study communities were conventional such as beer, whisky, or locally made. Locally produced beverages included "arki" ("Odontol", "Hah", ...) and palm wine. The bark, sap or fruit of plants adjuvant are known to contain alkaloids and tannins which are potent neurotropic substances. The likelihood of developing SAE among cases and controls did not differ significantly with history of consumption of alcoholic beverages. Nor did it differ for other indicators of chronic alcohol consumption.

Keywords: Alcohol consumption, onchocerciasis, audit, serious adverse events, encephalopathy.

INTRODUCTION

Human onchocerciasis is a public health problem and an obstacle to socioeconomic development in endemic countries of Africa, Arabian Peninsula and South America (WHO, 1995). The community-directed treatment with ivermectin (CDTI) is the main strategy adopted by the Afri-can Programme for Onchocerciasis control (APOC). Seve-re adverse events (SAEs) have been associated with mass treatment with ivermectin in areas where *Loa loa* and onchocerciasis are co-endemic (Duke, 2003; Twum-Danso, 2003). This has caused wide spread concern on the sustainability of CDTI (Amazigo et al., 2002; Addiss et al., 2003). The pathogenesis of *Loa loa* encephalopathy is not fully understood, but the primary determinant is the level of *Loa loa* microfilaraemia (Gardon et al., 1997; Boussinesq et al., 1998; Gardon et al., 1999; Boussinesq et al., 2001) and the inflammatory pathogenesis related to the dying worms (McGarry et al., 2003). Field observations have pointed out the effect of alcohol as a co-factor in the determination of SAE, but the information available is conflictive. Food and alcohol are known to alter ivermectin bio-availability (Baraka et al., 1996). The contra-indication of alcohol consumption around Mectizan intake as indicated by Merck and Co., Inc. have safety concerns, but may unnecessarily deter some people from taking ivermectin (The Mectizan Expert Committee, 2000). Shu et al. (2000) failed to establish any enhanced occurrence of side effects in patients who consumed

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Table 1. Age distribution of cases of severe adverse events to mectizan and their controls.

Age (in years)	Cases	Controls
Less than 20	7 (19.4 %)	7 (16.3 %)
21-40	17 (47.2 %)	17 (39.5 %)
Above 40	12 (33.3 %)	19 (44.2 %)
Total	36 (45.6 %)	43 (54.4 %)

Table 2. Distribution of cases of Severe Adverse Events to Mectizan and their controls by sex

Sex	Cases	Controls
Males	25 (69.4 %)	24 (55.8 %)
Females	11 (30.6 %)	19 (44.2 %)
Total	36 (45.6 %)	43 (54.4 %)

alcohol. The alcoholic content of the beverages used was low (Star beer: 4.5% v/v alcohol), compared to the alcoholic beverages and spirits that are consumed in most rural communities. The local beverages of Cameroon are produced from uncontrolled fermentation, with obviously higher alcohol content and diversity. Indicators of alcohol use are the level of transaminase and clinical, social and behavioral indicators that can be assessed by biochemical tests and the Alcohol Use Disorder Identification Test (AUDIT). Serum gamma-glutamyl transferase (GT) and serum aspartate amino transferase (AST) are common laboratory tests likely to provide an indication of alcohol consumption (WHO, 1992) . The present study was a case-control study designed to assess the contribution of alcohol intake to severe adverse events following mass distribution of ivermectin.

MATERIALS AND METHODS

Study area

The study was carried out in health districts of Bankim (in the savannah zone), and of Nanga Eboko, Obala, Okola and Sa'a in the forest-savannah transition zone, where cases of severe adverse events (SAE) were reported during mass distribution of ivermectin between January and July 2003.

Methods of investigation

Investigations were carried out on days 1 - 10 days after mass distribution of ivermectin. The national reporting system for SAE was used to locate and trace cases. All cases of SAE and their controls were assessed and blood samples collected to determine the level of serum transaminases. "Controls" subjects of the same sex and village were selected from the Community distributor's registers among individuals, aged within 5 years gap, who had taken ivermectin and did not experience any adverse reaction. The 10-items of the Alcohol Use Disorder Identification Test (AUDIT) questionnaire was addressed to study participants (WHO, 1992). When required, we interviewed the legal guardians of SAE patients. Questions were related to the history of alcohol consumption 24 hours around ivermectin intake. An in-depth interview was conducted with regard to the type of beverage and spirit consumed. The study received ethical clearance from the ethical review committee of the Faculty of Medicine and Biomedical Sciences and of the National Ethical Committee of Cameroon. Each participating subject provided informed consent before the interview and blood collection. All examinations and specimen collection were conducted taking necessary precautions to avoid the transmission of infections, including HIV and hepatitis B virus through needles and syringes. All used needles, syringes were decontaminated prior to disposal in a pit.

Data collection and analysis

Data were centralized in a computer and analyzed using the EPI INFO software. Interpretation of the AUDIT data followed standard proce-dures (WHO, 1992). Scores on items 1 - 3 in the absence of elevated scores on the remaining items was defined as hazardous alcohol use. Elevated scores on items 4 - 6 implied alcohol dependence. High scores on items 7 - 10 were interpreted as harmful alcohol use. Appropriate statistical methods were used to determine if alcohol consumption was a risk factor for SAE.

In depth interview of key informants were taped, transcribed and analyzed using the content analysis method (Groupe de Recherche Chari, 2001).

RESULTS

During the study period, the National SAE surveillance system reported 36 cases of SAE in CDTI areas. Matched controls (43) were identified for a total of 79 participants.

Socio-demographic characteristics of study subjects

Most SAE cases were aged 21 - 40 years. The age and sex distribution of participants did not differ between cases and controls (Table 1). Males were two times more likely to be SAE cases than females (Table 2).

Alcohol consumption around mectizan distribution

The number of days from the last alcohol consumption prior to Mectizan intake ranged from zero to 6 months. (10) participants had consumed alcohol within 24 h prior to Mectizan intake. Two of them were cases of SAE and 8 were controls (Table 3). The time of last alcohol intake was independent of the occurrence of SAE (OR = 0.26, p = 0.16).

Types of alcoholic beverage consumed around Mectizan distribution

The standard alcoholic beverages consumed were beers such as 33 Export (5% v/v), Mutzig (5.4% v/v), Beaufort

Table 3. Association between indicators of alcohol consumption and severe adverse events.

Consumption of alcoholic beverage	Cases (n/N)	Controls (n/N)	OR (CI)	p
Within last 24 hours	2/34	8/35	0.26 (0.03<OR<1.46)	0.16
Ever consumed	10/27	6/38	0.39 (0.10<OR<1.51)	0.20

Table 4. Plant adjuvants of palm and raphia wine in the Bankim, Nanga Eboko, Obala, Okola and Saá Health Districts (January - August 2003).

Health District	Local name	Scientific name	Family name	Part used	Active ingredients
Bankim	None				
Nanga Eboko	Noix de palme	*Elaeis guinense*	Areceae	Fruit	Alkaloids, tannins
	Essock	*Garcinia lucida*	Clusiaceae	Bark	Tannins
	Ndoung	*Seiba pentandra*	Bombaceae	Bark	Not assessed
	Ebak = ebak elong	*Brideria ferruginia*	Euphorbiaceae	Bark	Alkaloids, tannins
	Onieh = bitter kola	*Garcinia kola*	Clusiaceae	Bark	Alkaloids, tannins
Obala	Ebak = ebak elong	*Brideria ferruginia*	Euphorbiaceae	Bark	Alkaloids, tannins
	Onieh = bitter kola	*Garcinia kola*	Clusiaceae	Bark	Alkaloids, tannins
	Mbami[1] = Mbarbi = lianes	*Paullinia pinnata*	Salpindaceaea	Sap	Alkaloids, tannins, saponins
	Cacoa	*Theobroma cacao*	Sterculiaceae	Roots	alkaloids, theobromine
	Canabis				
Okola	Ebak=ebak elong	*Brideria ferruginia*	Euphorbiaceae	Bark	Alkaloids, tannins
	Onieh=bitter kola	*Garcinia kola*	Clusiaceae	Bark	Alkaloids, tannins
	Mbami=Mbarbi=lianes	*Paullinia pinnata*	Salpindaceaea	Sap	Alkaloids, tannins, saponins
	Cacoa	*Theobroma cacao*	Sterculiaceae	Roots	alkaloids, theobromine
	Canabis				

[1]The consumption of parts of this plant causes headache

Table 5. Association between the degree of alcohol use and the occurrence of Severe Adverse Events

Degree of use	Cases	Controls
No use	10 (27.8 %)	6 (14.6 %)
Dependent, Harmful or Hazardous use	26 (72.0 %)	37 (86.3 %)

OR = 0.42 0.68 <CI<8.52, p = 0.21

(4.6% v/v), Tuborg (5.6 % v/v), Castel (5.2 % v/v), Castle (6 % v/v), Guinness,...), red wine such as Vinosol, Gandia, ...(12% v/v), gin “Nofia”. Palm and raphia wine were the most commonly used alcoholic beverages in the study localities**.** The alcohol content of palm and raphia wine is generally low. Some plant adjuvants are used during the taping process to give palm wine a bitter or a rhum-like taste (Table 4). Some of the plants fruits, bark, roots and sap contain alcaloids and tanins that are potent on the cardiovascular system and possibly on the nervous system. The consumption of parts of *Paullinia pinnata* (Salpindaceae) is locally known to cause headache. The local gin “Arki”, “Odontol”, “Hah”, “Fort”) produced from banana, sugar cane or cassava tubers is a product of uncontrolled fermentation.

Comparaison of the AUDIT score among cases and controls

The rate of SAE was 2.37 times higher among dependent alcohol users than in non-users (0R = 2.37, 0.68<CI<8.52), but not among cases and controls (Chi-Square = 1.54, p = 0.21) (Table 5).

Serum transaminases as indicators of chronic alcoholism

The mean and median levels of SGOT did not differ signify-cantly among males and females (Kruskal-Wallis H = 0.27, p = 0.6) (Figure 1). No significant difference was observed when serum GGT (Kruskal-Wallis H = 0.93, p = 0.33) or SGPT (Kruskal-Wallis H = 0.12, p = 0.72) when compared between cases and controls (Figure 2 and 3).

DISCUSSION

The age and sex related susceptibility to SAE may be

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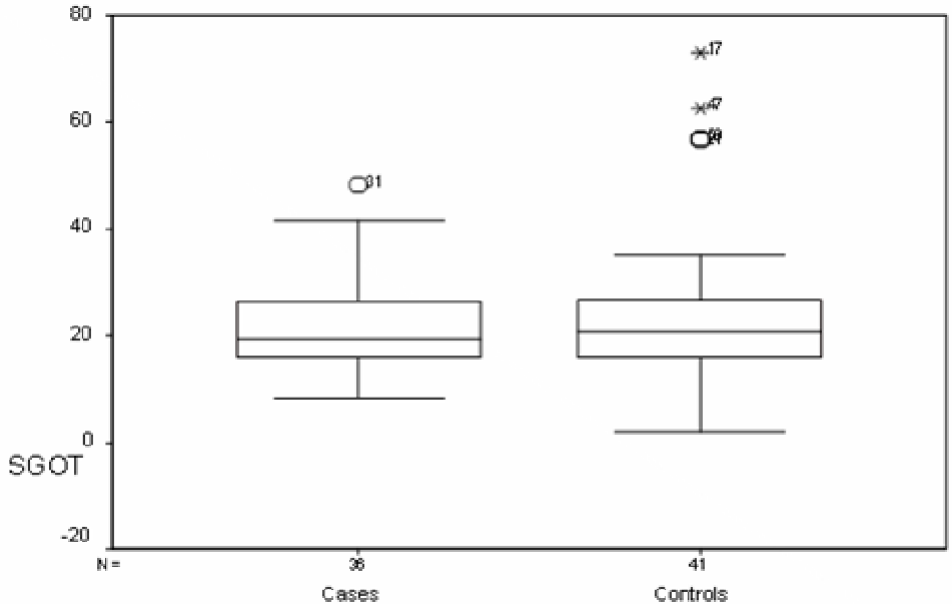

Figure 1. Distribution of the level of serum glutamyl oxaloacetate transferase (SGOT) among cases of SAE and Controls.

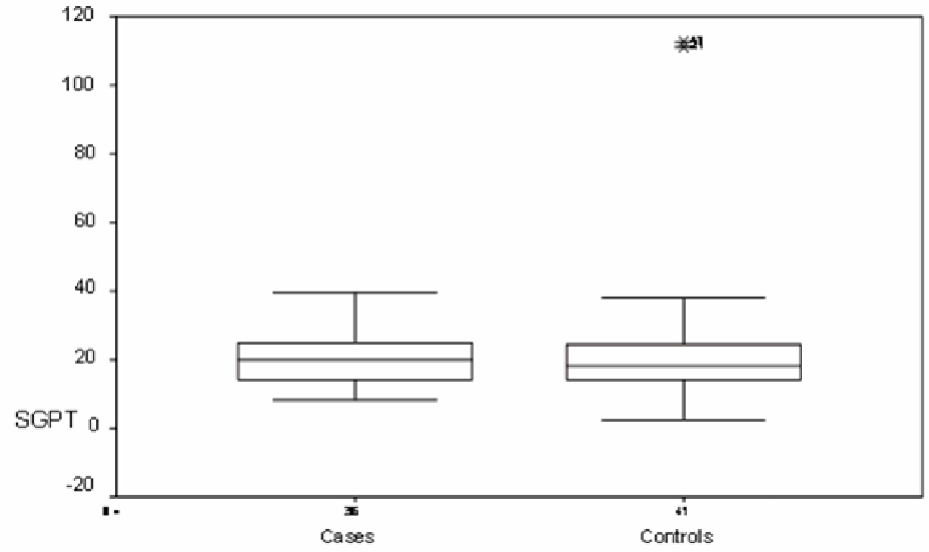

Figure 2. Distribution of the level of serum glutamyl phosphate transferase (SGPT) among cases of SAE and controls.

associated with the fact that males and adults are more likely to harbour high microfilaraemia (Kamgno and Boussinesq, 2001).

The fact that about one eighth of the respondents acknowledged having drank alcoholic beverages depicts the fact that the recommendation not to drink that is given by CDDs is not fully complied with. Anecdotal reports account that some individuals refuse to take Mectizan when abstinence to alcohol is requested. The occurrence of SAE is not associated with the timing of the last alcohol consumption, indicating that alcohol intake is not a major determinant of SAE. Because of the limited number of cases, we did not separate the different types of alcohols consumed. High content distilled alcohols may

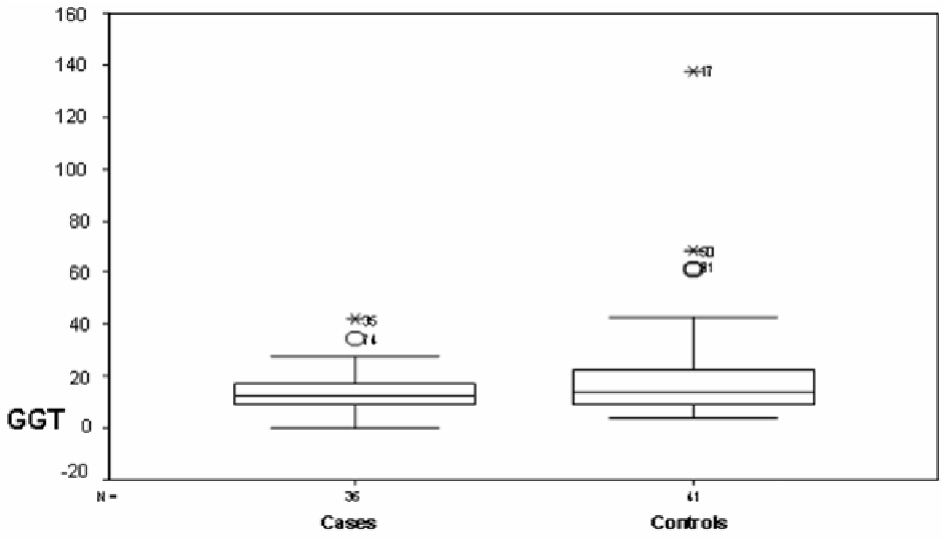

Figure 3. Distribution of the level of serum gamma-glutamyl transferase (GGT) among cases of SAE and controls.

may contribute to SAE, as these beverages contain a variety of alcohols which may be neurotoxic. Still the local palm wine and raphia wine are blended with plant adjuvants, some of which may be potent neurotoxics. The plant *P. pinnata (Salpindaceae)* – locally called 'Mbami', 'Mbarbi' or 'lianes' – is known to cause head ache. The influence of these adjuvants as determinants of SAE deserves further investigations.

The AUDIT questionnaire has been widely used in the investigation of alcohol use and abuse. There was an absence of relationship between alcohol consumption and SAE. It is possible that some of our participants (cases) could have denied alcohol consumption for fear of loosing the coverage of hospital costs as practiced by the National Onchocerciasis Control Programme.

The independence of alcohol used to SAE was also depicted by non elevated levels of serum glutamyl oxaloacetate transferase (SGOT), glutamyl phosphate transferase (SGPT) and gamma glutamyl transferase (GGT). which are biochemical markers of alcohol abuse (Stout, 1999; Braun et al., 2003).

The primary factor involved in SAE remains the high *Loa loa* microfilareamia (Boussinesq et al., 2001). Alcohol use and abuse may however contribute to ill health through several mechanisms, one of determinants being the type of alcoholic beverage. Ethanol that is found in beverages may not be a key factor in SAE (Shu et al., 2000), but other alcohols such as methanol or buthanol of the locally produced "Arki", "Odontol" or "Hah" could contri-bute. The plant adjuvants of beverages may be at least co-factors. In one instance, a community distributor in the Okola health district reported that a patient who developed SAE had ingested palm wine after ivermectin treatment. A similar case was quoted by Boussinesq et al. (2003). While there is an increased bioavailability of ivermectin following the co-administration of ivermectin with ethanol (Edwards et al., 1988; Cerkvenik and Grabnar, 2002), it is unlikely that the level of Ivermectin reached is enough to cause SAE. The adjuvants of palm wine reported in the present investigations contain tannins, alkaloids and saponins which are all potent on the nervous system. Tannins increase the resistance, reduce capillary permeability of red blood cells and are vasoconstrictor of blood vessels. Vasoconstriction of the extracranial arteries causes headache, restlessness and dizziness. Saponins are characterised by their tensio-active properties. Many saponins speed up haemoglobin degradation through their interaction with sterols of the membrane of the red blood cells. Alkaloids are complex nitrogenous substances with a bitter taste, that which is most preferred by consumers of palm wine. Alkaloids can be stimulants or depressors of the central nervous system (Bruneton, 1999).

The consistence of the AUDIT questionnaire and the serum transaminases analyses indicate the independence of ethanol containing alcoholic beverage consumption from the occurrence of SAE.

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